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MAY 1955

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Use of Large Doses of Cortisone in Schizophrenia

Clinical, Physiological, and Metabolic Observations

PHILLIP POLATIN, M.D.
STANLEY LESSE, M.D.
and
MEYER M. HARRIS, M.D.,† New York

The purpose of this investigation was to assay the effects of large doses of cortisone in known schizophenics, who, for the most part, were resistive to other forms of therapy. Since Hench, Kendall, Slocum, and Polley [1] first published their paper in April, 1949, on the use of cortisone in rheumatoid arthritic patients, literally hundreds of investigators have reported on the psychological changes secondary to the administration of cortisone for the treatment of various primary organic and psychosomatic illnesses. In most instances it is difficult to tell whether the psychic changes reported were due to the direct action of the hormone drug itself or represented secondary effects arising from alterations in the organic disease processes.

Relatively few studies were reported on the cortisone treatment of patients with psychiatric disturbances. In 1951, Cohn and associates * reported that cortisone produced very favorable results in some refractory schizophrenic patients. Also, it apparently enhanced the effects of electroshock therapy when given in conjunction with the cortisone. The very encouraging reports of Cohn and associates, who later gave their patients massive doses of cortisone,[4] and the general lack of knowledge of the effects of cortisone on schizophrenic patients stimulated this present investigation.

The patients observed for this study were admitted on a voluntary basis, were, for the most part, entirely cooperative to the research regimen, and were mainly in good contact, with no sensorial defects.

MATERIAL AND METHODS

Nine women patients, ranging in age from 19 to 42 years, all presenting schizophrenic patterns of different subtypes, were studied from 4 to 10 weeks each. During this period they received a daily dose of 500 mg. of cortisone either by mouth or by intramuscular injection, mainly by mouth.

All patients were studied psychiatrically and physically several times per week. This was in addition to the routine psychotherapy received by every patient. Initially the following studies were performed prior to the onset of cortisone therapy: (1) daily vital signs and weight observations; (2) complete blood count and urinalysis; (3) glucose tolerance tests; determinations of (4) serum sodium, (5) serum potassium, (6) blood chlorides, and (7) carbon-dioxide-combining power; (8) eosinophile counts; (9) basal metabolic studies; (10) electrocardiography; (11) electroencephalography; (12) chest x-ray studies.

The following laboratory procedures were carried out during the course of treatment:

1. Daily
   (*a*) Vital signs recorded before patient arose from bed
   (*b*) Weight taken before breakfast
2. Twice per week
   Eosinophile counts (before breakfast)
3. Weekly
   (*a*) Complete blood count
   (*b*) Urinalysis
   (*c*) Blood chemistry
      (1) Serum potassium
      (2) Serum sodium

The cortisone used in this work was supplied by Merck & Company, Inc., Rahway, N. J.

From the Departments of Clinical Psychiatry and Medicine, New York State Psychiatric Institute.

† Dr. Harris died Dec. 22, 1952.

* References 2 and 3.

(3) CO_2-combining power
(4) Blood chlorides
(5) Fasting blood sugar
(*d*) Electrocardiography

4. Every 10 days
(*a*) Electroencephalography
(*b*) Basal metabolic studies

Following the completion of the drug treatment, all the above tests, plus chest x-ray studies, were repeated on one or more occasions.

On the first day of treatment each patient received 10 tablets (25 mg. each) of cortisone (Compound E), or a total of 250 mg. in two equal doses. Every day thereafter 250 mg. was given before breakfast and another 250 mg. in midafternoon. A daily dosage of 500 mg. was maintained for a minimum of three weeks. In most instances 10 to 12 days were allowed for the gradual final withdrawal of the drug. Psychological, physical, and laboratory studies were continued for one month following the termination of cortisone therapy. In several instances electroshock therapy was added to the endocrine treatment.

REPORT OF CASES

The nine case reports follow.

CASE 1.—The patient was a 44-year-old, single white woman, admitted to the Psychiatric Institute Sept. 2, 1952. The history indicated that at the age of 15 she began to complain of constant headaches, throbbing in her feet, pains in her teeth, and hypersensitivity to noise. For many years, as the somatic symptoms became more and more frequent and more diffuse, she became increasingly incapacitated, going to numerous physicians, hospitals, and clinics. No organic basis for her many somatic symptoms was ever discovered. Throughout this period she held a series of jobs, which she left because of her inability to tolerate the noise in such objects as the fluorescent lamps and other electrical fixtures. Since the age of 28, she had had a series of unsatisfactory heterosexual relationships, mostly with older men. About five years prior to admission she began to feel that her symptoms had a psychological basis, and, after two short courses of unsuccessful psychotherapy, with two different psychiatrists, she sought admission to a psychiatric hospital in November, 1950, and remained there for about one and a half years.

During this first hospitalization she received intensive psychotherapy, to no avail, and finally a series of six electroshock treatments, which produced no favorable effects in her mental condition. When she returned home, her somatic complaints continued to be extremely diffuse and severe, incapacitating her completely. She would become tense and agitated and talked about suicide. She was unable to resume work, remaining in bed most of the day and acting in a very dependent, clinging manner.

In the Psychiatric Institute, a diagnosis of schizophrenia, mixed type with hypochondriasis, was made and she received intensive psychotherapy, with no favorable effects whatsoever. Cortisone was administered from Oct. 17 to Nov. 15, 1952, the patient receiving 500 mg. daily till the last week, when the dose was gradually decreased. With the cortisone there was an accentuation of the patient's anxiety and of all her hypochondriacal symptoms. She said, "On cortisone, I felt more apprehensive and tense. All my thoughts were exaggerated. I couldn't control myself as before. Cortisone acts like Benzedrine on me. It makes me jittery and gives me a hopped-up feeling." Toward the end of cortisone therapy there was a noticeable increase in psychomotor activity. There was marked restlessness; although the patient had complained of this feeling subjectively for the first three weeks, it was only during the last week that this symptom was objectively confirmed. After termination of therapy all of the patient's symptoms were increased subjectively.

In spite of the large dose of cortisone, no significant changes in vital signs were recorded. There was no weight gain in spite of the patient's being on a regular diet. The blood count and lymphocyte count remained unchanged. The eosinophile count dropped to less than 50% of the precortisone level but returned to the normal level by the time cortisone ingestion had been decreased to 100 mg. per day. All blood chemistry studies were consistently within a normal range before, during, and after cortisone therapy.

The patient's physical appearance revealed no changes at any time during the large intake of cortisone. There was no edema, no "moon face," no hirsutism, or any other alterations.

Basal metabolic studies before, during, and after treatment were essentially unchanged and were within normal limits.

Roentgen studies of the chest were similarly unchanged from normal readings.

The only electrocardiographic change was a slight sinus arrhythmia.

In general, the patient's mental condition showed no improvement.

CASE 2.—The patient was a 23-year-old, single white woman, admitted to the Psychiatric Institute on April 24, 1952. The history indicated that since early life the patient had manifested evidence of shyness, self-consciousness, and seclusiveness. She had great difficulty in adjusting to any life situation, such as in making friends, going to school, obtaining jobs, and engaging in social activities. About two years prior to admission she was given electroshock therapy, and after the fourth treatment

she developed an acute psychotic episode characterized by marked fear, bewilderment, agitation, and feelings of body dissolution. When the electroshock therapy was discontinued, she quickly recovered from this episode but continued to have feelings of unreality and became increasingly insecure, self-conscious, and seclusive.

In the Psychiatric Institute, a diagnosis of schizophrenia, simple type, was made, and the patient began treatment with insulin coma combined with electroshock from June 30 to Sept. 24, 1952. The patient received 66 insulin comas and 15 electroshock treatments. With this the patient became somewhat hypomanic, mildly euphoric, and rather silly. She socialized somewhat better, but about a week after termination of therapy she reverted to her extremely seclusive, shy, withdrawn behavior and began to wear dark glasses on the ward. She then began treatment with a combination of cortisone and electroshock from Oct. 31 to Dec. 22, 1952, receiving 500 mg. of cortisone daily and eight electroshock treatments. There was no sustained favorable effect from this treatment.

On the cortisone therapy, she began to manifest evidence of a modified Cushing syndrome about the 23d day, showing maximum signs about the 32d day, with symptoms of "moon face," male fat distribution, and hirsutism of the face and arms.

This picture subsided almost entirely 20 days after she had discontinued the cortisone.

Gradually, during the first 10 days of cortisone therapy there was a slow increase in weight, amounting to about 3 kg. (6.6 lb.). She was placed on a salt-poor diet at this point, and her weight decreased to about the pretreatment level.

About the 10th day moderate edema of the face, particularly periorbital edema, was noticed. Also, at this time, an increase of fat distribution was observed about the shoulder girdle, and the pelvic girdle fat seemed relatively diminished, giving her a more masculine contour.

Subjectively the patient complained of feeling more tense and anxious while taking the drug. Associated with this were marked feelings of depersonalization, an increase in withdrawal symptoms, and difficulty in "holding on to reality."

General behavior on the ward, in social activities, and in hospital routine was markedly impaired, the patient remained completely isolated and seclusive, participating in none of the usual daily activities, and remaining aloof from the group, doing practically nothing.

On the 25th day of cortisone therapy, she received her first electroshock treatment. In combination, she received a total of eight electroshocks, being given an electroshock treatment once weekly for the first two weeks and then three times weekly for the following two weeks. For a period of about a month, with the combination of cortisone therapy and electroshock, the patient seemed somewhat more alert and social, less tense, and in better contact. This improvement was very transitory and was entirely related to the introduction of electroshock, since this seeming improvement disappeared as soon as the electroshock therapy was discontinued.

In spite of weight gain and other modified Cushing-like physical signs, there was no significant increase in blood pressure before or after the introduction of the salt-poor diet. There was, also, no significant fluctuation in potassium, sodium, chloride, carbon-dioxide-combining power, or blood sugar levels throughout the whole course of cortisone therapy.

Serial eosinophile counts revealed an average drop of two-thirds of the pretreatment level; after cortisone was discontinued for one week, the eosinophile count returned to the normal pretreatment level.

The basal metabolic rate before cortisone was —10%. On the 14th day of cortisone therapy, the basal metabolic rate was —27% on two occasions in spite of a moderate increase in anxiety. Repeated tests remained approximately at the same lowered levels throughout the treatment procedure.

Pretreatment, treatment, and post-treatment electrocardiograms revealed no essential differences. They were all within normal limits, in spite of the fact that the patient developed a "modified" Cushing syndrome. No roentgen evidence of any pulmonary changes was observed.

CASE 3.—The patient was a 41-year-old, single white woman, admitted to the Psychiatric Institute on Sept. 4, 1952. The history indicated that the patient had always been a rather withdrawn, schizoid person. About nine years prior to admission, she developed ideas of persecution and ideas of reference. She became suspicious of her family, feeling that they were tampering with her mail and were doing things to harm her. She began psychotherapy about eight years prior to admission and then began to express delusional ideas that her psychiatrist was making nocturnal visits to her home for erotic reasons. She had had three previous hospitalizations in two private psychiatric hospitals from 1947 to 1952, with no improvement in her mental condition. In the six months prior to her present admission her ideas of persecution became very active. She accused members of her family of having her followed, of spying on her, and she began threatening her mother. A few weeks before admission she called the police to complain about an unknown person who, she alleged, was following her.

In the Psychiatric Institute, where a diagnosis of schizophrenia, paranoid type, was made, she was completely withdrawn, isolated, inactive, and quite uncooperative. She would talk to no one and

resented anyone who addressed her. On Sept. 28 she began treatment with cortisone by mouth, and on Oct. 30, 1952, this therapy was discontinued, after the patient had received 500 mg. of cortisone per day. There was no favorable change in her mental condition.

After the sixth day of cortisone treatment, with a weight gain of 4 lb., she was placed on a salt-poor diet. Throughout the cortisone treatment period, there was no significant alteration in blood pressure, nor were there any further significant physical signs often associated with cortisone therapy.

All blood studies were unaltered during the course of cortisone treatment. The eosinophile counts, surprisingly, did not manifest any significant drop.

Basal metabolic studies before and during treatment were essentially within normal limits.

No roentgen changes of the chest attributable to cortisone therapy were reported.

Electrocardiographic tracings showed a slight left axis shift throughout therapy.

Case 4.—The patient was a 25-year-old, divorced white woman, admitted to the Psychiatric Institute on Aug. 21, 1952. The history indicated that about a year prior to admission she began to feel tense, anxious, and apprehensive and began psychotherapy, attending two or three sessions weekly. After six months of treatment her therapist recommended hospitalization but the patient refused. About three weeks prior to admission, she became extremely tense and agitated, approached her mother, unbuttoned her mother's blouse, and began to suckle at her mother's breast, stating, "I must know if you are my mother or if my grandmother is my mother." She was immediately admitted to Bellevue Psychiatric Hospital, where she expressed feelings of unreality and was extremely tense, irritable, and hostile; from there she was transferred to the Psychiatric Institute, which she entered as a voluntary patient. Attempts at psychotherapy resulted in no noticeable change in her mental condition. She remained extremely tense, seclusive, and completely withdrawn and preoccupied. There was a depressive element, and she expressed ideas of hopelessness. She verbalized somatic delusions and felt that one side of her body was entirely different from the other side. A diagnosis of schizophrenia, mixed type, was made. On Oct. 31, 1952, she began treatment with cortisone, receiving 500 mg. daily until Nov. 22, at which point the cortisone dosage was decreased gradually until Dec. 6, 1952, when the drug was discontinued completely. There was no favorable change in her mental condition.

By the fourth day of cortisone therapy the patient seemed more tense and anxious and stated that she felt worse. By the eighth day of cortisone she was so extremely tense that she began to have shaking spells. After 15 days of cortisone therapy she was confused, out of contact, paced the floor continuously, and began masturbating openly. The entire psychiatric condition had worsened.

Between the 21st and the 32d day of treatment, the patient made four impulsive suicidal attempts. She was extremely negativistic and paranoid, manifesting sudden unmotivated and uncontrolled temper outbursts. She became incontinent of urine. The patient presented primitive, archaic thinking, speaking in symbols and complaining of hyperacusis. "Stop the noise; everything is so loud to me."

On the 21st day, the gradual process of cutting down the high cortisone dosage was begun in slow stages, so that by the 36th day of treatment the patient received 25 mg. of cortisone and therapy was terminated. At this point her psychotic symptoms were still very active.

About three days after all medication was terminated, the patient seemed more relaxed and more cheerful, with subsidence of gross psychotic manifestations. She stated that she felt much better. Four days later (seven days after cessation of cortisone) all psychotic symptoms reappeared, but to a milder degree than was observed during cortisone therapy.

Prior to her discharge from the hospital, the patient volunteered the remark that while on cortisone therapy, " I felt I was losing control."

Interestingly enough, in spite of a marked psychotic state observed during cortisone therapy, the only physiological alteration was a change from a pretreatment hypotensive state to a normotensive level during treatment, with a return to the pretreatment hypotensive condition after cortisone was discontinued.

There was no weight increase, even though the patient maintained a regular diet throughout the treatment period. Neither were there any other physical signs usually associated with hyperadrenalism. The eosinophile count on drug therapy dropped about 50% and remained there until cortisone was discontinued, within two days returning to normal levels.

There were no significant electrolyte alterations. Basal metabolic studies and roentgen examinations of the chest were entirely within normal limits. Electrocardiographic tracings revealed no significant alterations during the course of therapy.

Case 5.—Patient was a 36-year-old, married white woman, admitted to the Psychiatric Institute on July 23, 1952, with a diagnosis of schizophrenia, depressed type. The history indicated that for the past three or four years the patient had been extremely withdrawn, incapable of taking care of herself, her house, or her children, and manifesting intense preoccupation, remaining in bed for days at a time, with periods of depression and agitation. She had

been separated from her husband for many years and was living with her two children and her mother.

The patient was started on cortisone therapy on Sept. 12, 1952. Between the 20th and the 32d day of cortisone treatment, the patient received six electroshock treatments in combination with smaller doses of cortisone.

During the 20-day period of cortisone therapy alone, the patient showed only slight objective improvement, in that she did not weep as much and was less tremulous. Subjectively, however, the patient stated that she felt just as bad as before. Suicidal preoccupations and inner tensions were unabated.

When electroshock therapy was added to a progressively decreasing amount of cortisone, there was a noticeable improvement in the patient's work and social adjustment on the ward. The patient felt much less depressed, and her suicidal preoccupations were alleviated.

All cortisone medication was discontinued on Oct. 17, after the patient had been on the drug for 36 days. By Oct. 24, depression and suicidal thoughts were again in the foreground, and by Oct. 27, that is, 10 days after cessation of cortisone and 14 days after the last electroshock treatment, the patient was again in a complete state of relapse.

With respect to her physical status, the patient showed no noticeable edema, no changes in fat distribution, or other manifestations commonly associated with adrenal cortex therapy. After she had been on 500 mg. of cortisone per day for three days, a 40 mm. of mercury increase in systolic blood pressure was noticed, together with a 15 mm of mercury increase in diastolic pressure. At the same time, a 3 lb. weight loss was experienced. A high caloric diet was given the patient, and by the 14th day of treatment she weighed 2 lb. more than her pretreatment weight. She was given a salt-poor diet for a period of 10 days, and her weight returned to that observed before treatment started. There were no significant changes in her blood counts. Electrolyte studies, blood sugar, and carbon-dioxide-combining power manifested no noticeable changes or abnormalities. There was no significant drop in the eosinophile counts during the entire course of treatment.

Basal metabolic studies before, during, and after cortisone therapy revealed no essential changes, and all were essentially within normal limits.

Roentgen examinations of the chest revealed no pathological changes.

The electrocardiographic findings revealed a slight tendency to left axis deviation during cortisone treatment.

It was interesting to note that this patient's psoriasis completely cleared during the course of cortisone therapy, and when cortisone was discontinued, the psoriasis returned.

CASE 6.—The patient was a 19-year-old, single white woman, admitted to the Psychiatric Institute on Dec. 21, 1951, with a diagnosis of schizophrenia, catatonic type. The history indicated that about two years prior to admission the patient had had a previous schizophrenic episode, from which she never completely recovered. On admission she presented somatic delusions, grimacing, posturing, screaming, and loss of contact. Her conversation was scattered, fragmentary, and bizarre, with marked dissociation between affects and ideas. She presented olfactory and visual hallucinations. Several weeks after admission she developed a two-day catatonic stupor, which changed to an acutely disturbed state in which the patient was impulsively assaultive and very destructive. She would then revert to an intensely preoccupied, withdrawn episode. These attacks would vacillate often.

Beginning Sept. 27, 1952, the patient received two courses of cortisone therapy, the first from Sept. 27 to Oct. 30, 1952, and the second from Dec. 1, 1952, to Jan. 22, 1953.

At the onset of cortisone therapy the patient was markedly withdrawn, unresponsive, preoccupied, and tense, with rigid affect, posturing, and response to auditory hallucinations. After nine days of therapy, moderate improvement was noted in that the patient appeared to be in better contact, somewhat more cooperative, and more sociable, with improved general performance.

On the 18th and 20th days of cortisone, electroshock therapy was given for those two days only. This produced a marked improvement in the patient's general condition, in that she was quite sociable, entirely cooperative, and amenable to all ward activities. This improvement continued, so that even though cortisone dosage was gradually decreased, beginning on the 18th day of treatment until the drug was entirely discontinued, on the 36th day of treatment, the patient stated, "I feel better than at any other time in the hospital." The improvement, however, was short-lived. Five days after the discontinuance of cortisone, the patient was again in a catatonic stupor. At this point (without any cortisone whatever) she was given five electroshock treatments over a period of 10 days. The psychotic episode disappeared, and the patient appeared to function at the relatively high level noticed previously on the combination of cortisone and shock therapy. About one week after the discontinuance of E. C. T. alone, the patient again reverted to her catatonic state. At this point (Dec. 1, 1952) the patient was again started on high doses of cortisone according to the technique previously described, and electroshock treatment was given concurrently once per week. In other words, 500 mg. of cortisone was administered daily in combination

with one E. C. T. per week. On this regimen there was some improvement, but not to the marked degree observed when the patient was given three E. C. T.'s per week, either alone or in combination with cortisone. After 53 days of this combined treatment, cortisone was terminated. The patient had received 500 mg. of cortisone daily for 40 continuous days, after which the dose was gradually decearsed, till, at the end of 53 days, the cortisone was discontinued. During these 53 days she received eight electroshock treatments in combination with cortisone.

During the first course of treatment with cortisone, lasting 33 days, the patient showed the following physiological changes: (1) an 8 lb. weight gain, and (2) a 20-point increase in systolic blood pressure without any concomitant increase in diastolic pressure. No changes in body contour were observed during this period. She was placed on a salt-poor diet, and the weight gain and systolic blood pressure increase disappeared.

During the second course of cortisone, lasting 53 days, a regular diet was given, without any salt restriction. During this period, the patient gained 14 lb., and again a 20-point increase in systolic blood pressure was noticed, without any significant diastolic increase.

Along with this, there was moderate to marked edema about the face ("moon face"), pitting edema of the ankles, and increase in facial hirsutism.

During the first series of cortisone the eosinophile count dropped on the average of more than 50% and returned to approximately the pretreatment level when cortisone was discontinued.

During the second series of cortisone we could not elicit any clear trend in the eosinophile counts. On certain days counts were less than 50% of the original pretreatment figure, while on other days no significant drop in eosinophile counts were observed. During the second series, when the patient was showing considerable somatic change, a high relative lymphocytosis was repeatedly observed.

Electrolyte studies, carbon-dioxide-combining power, and blood sugar studies were not significantly affected at any time.

The basal metabolic studies revealed no significant variations from the normal on cortisone therapy.

A slight tendency to left axis deviation was noticed on the electrocardiogram.

No roentgen abnormalities of the chest were reported.

Case 7.—The patient was a 25-year-old, married white woman, admitted to the Psychiatric Institute on Dec. 23, 1952, with a diagnosis of schizophrenia, paranoid type. The history indicated that the patient had always been a schizoid, withdrawn, and very dependent person. Two years before admission there was considerable depression and weeping prior to her marriage. After marriage, ideas of reference and paranoid symptoms became very marked; the patient accused her husband of infidelity and stated that people were talking about her behind her back and laughing at her. She began treatment with cortisone on Jan. 7, 1953, receiving 500 mg. daily until Jan. 22, when the dose was gradually decreased until discontinued on Feb. 5, 1953.

Cortisone therapy caused a marked increase in the patient's manifest anxiety and apprehension. She regressed to a markedly infantile level. She had to be dressed, undressed, and bathed; appeared constantly bewildered, and often screamed wildly without provocation and without words. Cortisone medication had to be administered parenterally because of her complete lack of cooperation, and consequently the tapering-off period occurred earlier and continued for a longer period of time.

Physiologically, a 6 lb. weight gain was noted after eight days of treatment, in spite of a marked decrease in food intake. Even after a salt-poor diet had been instituted, an additional 4 lb. weight gain was observed in the next five days. After 20 days of a salt-poor diet, weight returned to normal. Aside from the abdominal thickening, no somatic changes commonly associated with the administration of cortisone were noted.

Vital signs were not significantly altered by the medication. Eosinophile counts decreased to slightly less than 50% of normal and returned to pretreatment levels by the time patient was receiving 25 mg. of cortisone per day. All electrolyte and other blood studies showed no significant alterations.

Case 8.—The patient was a 35-year-old, single white woman, admitted to the Psychiatric Institute on July 12, 1952, with a diagnosis of schizophrenia, mixed type. She complained of innumerable physical ailments, many phobias, depressive feelings, and a general diffuse, intense anxiety, and manifested tremendous dependency on her sister and mother. All symptoms had been present for the preceding 10 years.

In the hospital the patient received a course of cortisone therapy from Nov. 4, 1952, to Dec. 12, 1952, with a daily dose of about 500 mg. Cortisone therapy produced a moderate increase in the patient's anxiety and depression. Subjectively she felt worse. Her ward and social performance became poorer. The patient stated, "Cortisone accentuates everything you ordinarily feel. If you feel crazy in the head, you feel crazier. You feel constant stirring up inside. My physical symptoms all increased and everything was frightening. It's a sort of hopped-up feeling, but very unpleasant."

On the 22d day of therapy the patient developed nausea, followed by vomiting of copious amounts of coffee-ground gastric content. This was accom-

panied by severe, cramp-like abdominal pains. This episode seemed to be due to an exacerbation of an old healed duodenal ulcer. An upper gastrointestinal series of x-rays confirmed this impression.

The cortisone dosage was decreased as rapidly as was considered feasible, and the patient was off cortisone completely within two weeks of the onset of gastric symptoms. The patient responded quickly to a full ulcer regimen, and another series of x-rays taken four months later revealed complete healing of the ulcer.

After six days of cortisone therapy the patient gained 7 lb.; she was placed on a salt-poor diet, and this prevented any further weight gain. Moderately severe ankle edema was observed at this time. The patient's usual complaint of easy fatigability was markedly increased throughout treatment with cortisone. No other physical signs usually related to cortisone therapy were seen. Vital signs were unaffected. Blood counts remained normal. Serial eosinophile counts did not reveal the usual drop. Blood chemistry findings were all within normal limits.

CASE 9.—The patient was a 22-year-old, single white woman, admitted to the Psychiatric Institute on June 17, 1952, with a diagnosis of schizophrenia, paranoid type. The history indicated that the patient had always been a withdrawn, schizoid type of person. In the spring of 1952 she began to manifest an excited state, in which she felt that people were reading her mind, that she could influence other people's thoughts, and that "they" might be spying on her through the bathroom window.

In the hospital she was given a course of cortisone therapy from Sept. 27 to Dec. 22, 1952, receiving approximately 500 mg. of cortisone by mouth per day.

Initially, during the first two weeks of treatment with cortisone, the patient appeared more anxious and depressed, and her ward and social behavior seemed very poor indeed. After 14 days of treatment, the patient remarked, "I feel all hopped-up but my symptoms seem about the same."

It was during the third week of treatment that a marked decrease in anxiety and depression was noticed and a pronounced favorable effect on ward and social behavior became evident. The patient stated that she felt more confident and more at ease.

On the 25th day of treatment the dose of cortisone was decreased, so that by the 35th day she was receiving only 50 mg. per day.

It was observed that when the cortisone dosage was decreased to 100 mg. per day or less, an acute paranoid, hallucinatory picture was seen with startling clarity. When the dosage was then increased to over 200 mg. per day, all psychotic manifestations disappeared.

For a second time, the psychotic picture returned when the cortisone was lowered to below 100 mg. per day. However, there was no remission of symptoms when the cortisone was again raised to levels up to 500 mg. per day. To repeat, it was interesting to note that on two occasions an increase of cortisone to above 200 mg. per day caused remission of psychosis, while on two occasions the decreased dose of cortisone to 100 mg. or less per day produced a marked exacerbation of the psychosis. On the third try, however, after the psychosis became severe with a lowered dosage, an increase to over 200 mg. of cortisone daily did not produce the previously observed amelioration of psychotic symptoms, and throughout the remainder of the therapy the patient remained actively psychotic. She said, "Cortisone brings my emotions to the fore and I can't handle them."

The only physical change noted was 4 lb. weight gain, and placing the patient on a salt-poor diet after 11 days of treatment produced a return of weight to the pretreatment level. Biochemical studies were all within normal limits except for the blood counts. After 14 days of treatment, a marked increase in lymphocyte counts with a proportional decrease in polymorphonuclear leucocytes was noted. This was observed as long as the patient was receiving more than 100 mg. of cortisone per day. While the patient was maintained on 100 mg. or less, a normal polymorphonuclear leucocyte-lymphocyte ratio was established.

Eosinophile counts dropped to approximately 50% of pretherapeutic levels and did not return to normal until the patient had been off therapy entirely for a few days.

Basal metabolic rates dropped from —12%, on the 10th treatment day, to —27%, on the 20th day of therapy with cortisone.

Electrocardiographic tracings revealed no changes of note except for slight sinus arrhythmia about the middle of the cortisone therapy.

COMMENT

REVIEW OF LITERATURE

On reviewing the literature on the psychoendocrinology of schizophrenia, particularly the role of corticotropin and cortisone, one is confronted with a mass of conflicting data. Hoagland † found that most schizophrenic patients are quantitatively subnormal in their adrenal stress responses and in responses to injected corticotropin as compared with normals.

This finding would seem to confirm the earlier anatomic impressions of Lewis of

† References 5 and 6.

generalized deficiency in size and weight of adrenals.[7] On the other hand, Altschule [8] reported that the responsiveness of the adrenal cortex in psychotics as measured by urinary excretion of 17-ketosteroids was the same as or slightly greater than the normal levels. In fact, he reported a decrease in excretion of urinary 17-ketosteroids as the patient improved. It was also reported by Altschule ‡ that there was no diminution in responsiveness to corticotropin in schizophrenics, irrespective of the duration of illness.

Cohn § reported outstanding results with cortisone in some patients who failed to respond to other therapies. They noted a marked synergistic relationship between cortisone and electroshock therapy, so that fewer electroshock treatments were required to produce favorable effects. They theorized that the cortisone was replacement therapy and that a drop in eosinophile count was accompanied by clinical improvement.

The results noted by Cohn are much more optimistic than those reported by others. Chance and associates [9] reported minimal differences between psychotic patients receiving cortisone and those on placebos. Gildea and associates [10] concluded that if psychotic patients are given large enough doses of cortisone, most of them will respond with transient increase in activity, a feeling of well-being, and partial remission of symptoms. While Gildea found no aggravation of symptoms, others || felt that deleterious effects on mood and symptoms could be produced with cortisone. Rees [13] reported that the patient could be protected from any severe psychiatric reactions by low-salt diet, high potassium intake, and adjustment of drug dosages.

Clinical Psychiatric Observations

Three of the nine patients showed slight or transient improvement. One, a schizophrenic adolescent in a catatonic stupor, demonstrated increased psychomotor activity, greater reality contact, and improved ward behavior, and she also related better in psychotherapeutic sessions. The improvement was very transient, for when the drug was discontinued all favorable effects disappeared. Reinstatement of cortisone therapy alone did not reestablish previous beneficial results.

A second patient, in a very severe schizophrenic depression with constant suicidal preoccupation, revealed definite objective affectual improvement, but subjectively there was no change. When electroshock was combined with the cortisone therapy, the improvement was enhanced, enabling the patient to socialize better, and even to visit home on two occasions. However, whatever improvement was observed soon disappeared. Since the same degree of symptom amelioration was observed with electroshock therapy alone, it was felt that the cortisone had little effect in the changes described above.

A third patient, who demonstrated pronounced paranoid mechanisms, showed accentuation of all symptoms during the first two weeks of cortisone, but after the third week was much less anxious, less depressed, and showed improved ward and social behavior. When the drug dose was decreased below 100 mg. per day, however, there was an exacerbation of symptoms. When the dose was increased to more than 200 mg. per day, the psychotic manifestations were again ameliorated. The psychosis was for a second time permitted to reappear by decreasing the drug dosage, but when the cortisone was increased on this third occasion, no beneficial effects were recorded.

Five of the nine patients became definitely worse on the cortisone therapy. In all these five patients a marked increase in anxiety and tension was the predominant manifestation. The effect was similar to that seen in some schizophrenics when given an intravenous amphetamine injection. Initially the patients all experienced an increase in psychomotor activity, followed by mounting tension and feelings of some impending disaster. Then the secondary defense mechanisms came into play (i. e., hypochondriasis, paranoid states, hallucinations, etc.). One patient regressed to the point where she was

‡ Altschule, M. D., in comment on Hoagland.[5]
§ References 2, 3, and 4.
|| References 11 and 12.

enuretic, masturbated openly, spoke in purely symbolic terms, had gross catatonic excitement followed by suicide attempts, and was dominated by paranoid delusions and hallucinations.

A second patient, after a period of mounting anxiety, regressed to an infantile level, in which she had to be bathed and fed and in which wild, uncontrolled screaming occurred.

A third patient, after a period of mounting anxiety, manifested a very pronounced increase in all hypochondriacal symptoms. Some difficulty with reality control was noted toward the last week on the drug. Similarly, a fourth patient, with the diagnosis of schizophrenia, mixed type, with pronounced hypochondriasis, showed a marked increase in her varied somatic complaints. As will be discussed below, this patient also had a recurrence of a duodenal ulcer.

One patient psychiatrically seemed to be completely unaffected by the cortisone.

It is of interest to note the patient's verbatim statements as to how they felt on the cortisone regimen.

"I feel I am losing control. I feel I have to keep moving. I'm jumpy. I feel like screaming and screeching."

"I feel more apprehensive and tense. It acts like Benzedrine on me. I can't control myself. It makes me jittery and gives me a hopped-up feeling."

"The drug accentuates everything you ordinarily feel. You feel crazier . . . speeded up inside. It's a sort of hopped-up feeling but very unpleasant."

"I had difficulty holding on to reality."

Three of our patients received a combination of cortisone and electroshock treatment. In the final analysis, it was not felt that the combination was in any way more effective than electroshock alone. Our experiences do not confirm the findings of Cohn and associates.¶

Somatic Alterations

Four of the patients showed significant weight gain. In three, the weight increased rapidly but declined when the patients were placed on salt-poor diets. As much as 10 lb. was gained in a two-week period. This weight gain was not associated with any increase in food consumption. One patient, early in therapy, lost weight, but this reversed itself without any alteration in regimen.

Six patients revealed clinically demonstrable physical changes. Two who were on a daily dose of 500 mg. of cortisone for six weeks demonstrated a modified Cushing syndrome after about 20 to 32 days of treatment. In one this was produced while she was on a salt-poor diet. She began to show physical changes about the 23d day of treatment, reaching a maximum on the 32d day. The first change was reported by the patient. She complained that her skirt band was tight (in the absence of any significant weight gain). A gradual rounding of the face was observed about the 25th day. The skin shortly thereafter took on a dusky-reddish hue, particularly over the cheeks and jowls. Between the 25th and 30th days, a dark, moderately heavy growth of hair appeared over the face, shoulders, and arms. The shoulder girdle appeared more fleshy, while the typical female pelvic fat was decreased. There was no hypertension, acne, keratosis pilaris, amenorrhea, or abdominal striae. A slight increase in muscle fatigability was recorded. No alkalosis or significant changes in carbohydrate metabolism were noted. Eosinophile counts, however, were less than half the pretreatment levels. A significant decrease in basal metabolic rate was also recorded. All physical changes disappeared in from two to three weeks after discontinuance of cortisone.

Case 6 also showed a modified Cushing syndrome. The patient was initially on cortisone for 35 days (with a salt-poor diet). During this period an 8 lb. weight gain was recorded, together with a 20 mm. increase in systolic blood pressure. Because of some initial psychiatric improvement, she was given a second period of treatment, lasting 52 days, this time on a regular diet. The patient gained 14 lb. After 22 days the patient's skirt band was tight on her. About the 28th day a pronounced rounding of the face, followed by a flush and hirsutism, was seen. The shoulder girdle appeared heavier, and the pelvic fat deposition showed some

¶ References 2 and 4.

alteration, presenting a masculine contour. Hirsutism was noted over the extremities. Some pitting ankle edema was found. A 20 mm. increase in systolic blood pressure without diastolic increase was again noted. During the first cortisone series a pronounced eosinophile drop was seen. This was not found in the second regimen. A rather paradoxical relative lymphocytosis was recorded on several counts. No electrolyte change or alteration in carbohydrate metabolism was detected.

The physical changes seen in the other patients were slight. Three complained of "thickening of the waist." In two this occurred without any significant weight gain. Two developed slight pitting ankle edema. A patient who was markedly hypotensive became normotensive during therapy and returned to original levels after removal of the drug. No amenorrhea was seen, contrary to many other reports. Instead, two patients had premature menses.

Case 8, who had a history of old duodenal ulcer, after 22 days of treatment suddenly complained of severe nausea, followed by vomiting of copious amounts of "coffee-ground" material. She was plagued by severe cramp-like epigastric pains. An upper gastrointestinal x-ray demonstrated an acute duodenal ulceration superimposed on a chronic lesion.

Alteration in Laboratory Studies

Several investigators [14] have reported that with the use of cortisone the eosinophile count drops 50% or more initially and that with continued use of the drug the eosinophile level gradually returns to a relatively normal reading. This we did not find in our studies.

Eosinophile counts dropped to levels 50% or more below the pretreatment figures in six patients. Three showed no significant changes in eosinophile levels. One patient while on a salt-poor regimen showed a marked eosinophile drop, but when on a regular diet manifested no significant change in eosinophile levels. A very slight leucocytosis was seen in several instances. Two patients showed a moderate to marked relative lymphocytosis, instead of an expected lymphopenia. In three other patients we found the more usual lymphopenia paralleling the decrease in eosinophile levels.

Not one of the patients demonstrated any significant changes in serum sodium, serum potassium, blood chlorides, carbon dioxide-combining power, cholesterol, or carbohydrate metabolism. Even those who demonstrated Cushing-like syndromes showed no alkalosis or diabetes mellitus.

Electrocardiographic tracings in a few instances revealed very mild left axis deviation (in the absence of any significant blood pressure changes). Basal metabolic studies were all within normal range except in two instances. Two patients showed levels of *—27%*, in spite of increasing anxiety. The recordings returned to normal after cessation of treatment.

All these results pose some very interesting and important questions. An explanation is wanting as to why only two patients in our series showed any pronounced evidence of hyperadrenalism in the face of prolonged massive doses of cortisone. Several explanations may be offered tentatively. There is the possibility that massive amounts of cortisone may produce an adverse reaction in the anterior pituitary, which, in turn, may inhibit normal pituitary-adrenal relationships.

Since nonschizophrenic patients, as far as we are able to determine, have never been exposed to massive cortisone therapy, we cannot predict definitely just how they might respond. That the endocrinological organization of some schizophrenics is such as to be uniquely refractory to massive doses of cortisone is a hypothesis that might well be proposed by some. It is our tentative feeling that the psychoendocrinological make-up of schizophrenics does not differ enough from that of normals to account in itself for our findings.

SUMMARY

Nine nondeteriorated schizophrenic women were given 500 mg. of cortisone daily for from 4 to 10 weeks. These patients were

studied intensively from the psychiatric, physical, and laboratory points of view.

1. Three patients showed slight and transient psychiatric improvement. Five were definitely made worse. One seemed unaffected. Many showed an increase in psychomotor activity.

2. No significant long-standing beneficial therapeutic results were obtained with use of cortisone alone. Cortisone did not appear to work synergistically with electroshock therapy.

3. Six patients revealed clinically demonstrable physical changes. Two showed a modified Cushing syndrome.

4. No significant alterations in electrolytes or other blood chemistry studies were seen. A significant eosinophile drop occurred in six patients. Two showed a significant drop in basal metabolic levels.

Several theoretical possibilities as to why all the patients did not show more pronounced evidence of hyperadrenalism are suggested.

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Epinephrine-Mecholyl Test (Funkenstein Test)

Its Value in Determining the Recovery Potential of Patients with Mental Disease

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This paper is based on a study of 201 consecutive patients seen in private practice during the past six years to whom Funkenstein's prognostic test [1] was administered prior to treatment. In a number of these patients the test was repeated at intervals during the course of, and after completion of, treatment. The subject of the present paper is the correlation of the pretreatment test results in these 201 cases with the outcome of the therapy chosen. The predictive value of the test was then subjected to statistical analysis.

This material is suited to test and validate the concepts developed by Funkenstein and associates [1] and amplified by Gellhorn [2] on a new sample.

The Funkenstein test consists in measuring the blood pressure changes and observing the immediate clinical and psychological response of the patient, first to an intravenous injection of 0.025 mg. of epinephrine, then to an intramuscular injection of 10 mg. of methacholine (Mecholyl) chloride.

The epinephrine test allows division of the patients into two major groups—those with and those without epinephrine-precipitable anxiety.

The Mecholyl test allows division of the patients into six fairly distinct groups based on their blood pressure response patterns. A seventh blood pressure reaction group is based on the epinephrine test; it consists of those whose blood pressure rise on intravenously injected epinephrine is inadequate.

Inadequate rise of blood pressure on intravenous injection of epinephrine is defined as a rise of less than 20 mm. Hg on injection of 0.025 mg., or of less than 50 mm. Hg on injection of 0.05 mg. of epinephrine. A moderate rise is defined as a rise of 20 to 40 mm. Hg on intravenous injection of 0.025 mg., or a rise of 50 to 75 mm. Hg on injection of 0.05 mg. of epinephrine. A marked rise is defined as a rise of 40-75 mm. Hg or more on intravenous injection of 0.025 mg., or a rise of 75-120 mm. Hg or more on injection of 0.05 mg. of epinephrine. To prevent such marked rises, both Funkenstein and I have reduced the standard test dose of 0.025 mg. of epinephrine except for the purpose of testing inadequacy of response to epinephrine, when the double dose can be given safely, after inadequate response has been established by the smaller dose.

The following description of the seven major blood pressure reaction groups, designated by Roman numerals, is given according to the definition introduced by Funkenstein and colleagues,[1] except for certain additional qualifying characteristics that have emerged in the course of my clinical experience with the Funkenstein test. These 7 groups, based on the blood pressure reaction pattern, actually comprise a division of the material into 14 groups, since each of the 7 major groups falls into 2 subgroups, one of them associated with the presence, the other with the absence, of epinephrine-precipitable anxiety. In the histograms illus-

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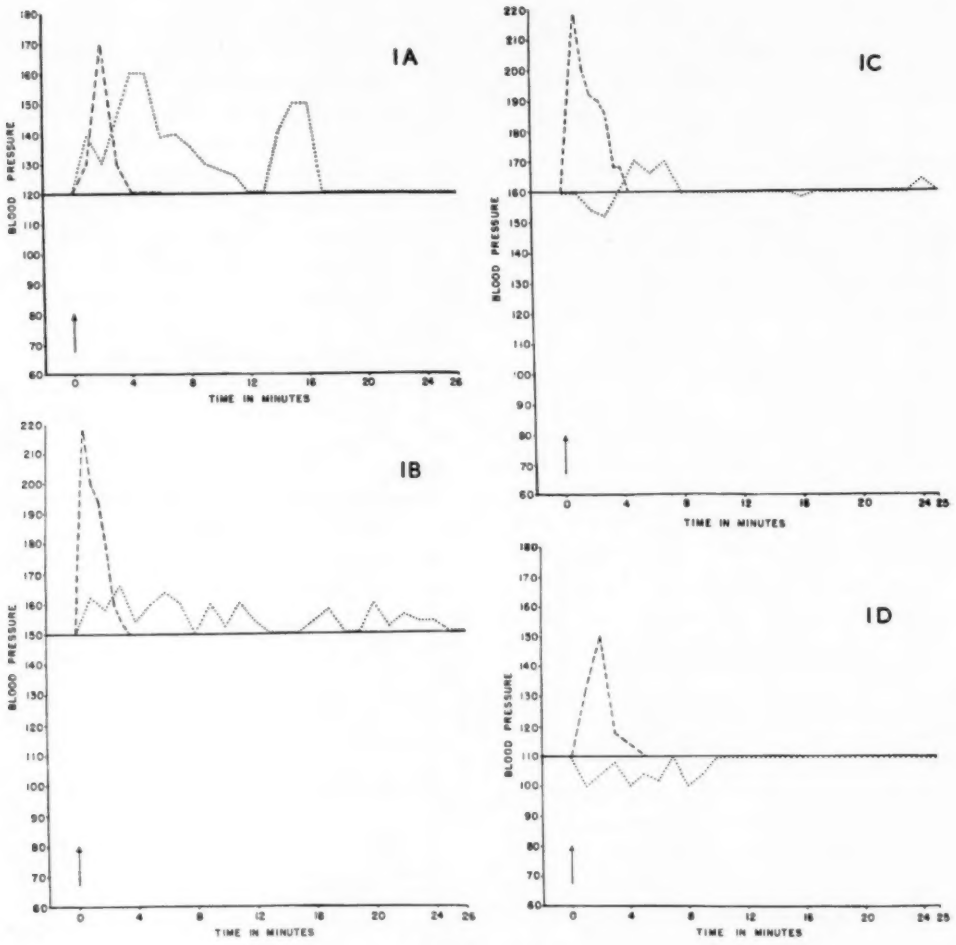

Figure 1—A to D

Fig. 1.—The blood pressure reaction types obtained by administration of epinephrine (0.025 mg. i.v.) (broken line), and by administration of Mecholyl (10 mg. i.m.) (dotted line).

A, Group I; *B*, Group I; *C*, Group II; *D*, Group III; *E*, Group IV; *F*, Group V; *G*, Group VI; H, Group VII (*E* to *H*, page 498).

trating this study, the subgroups with epinephrine-precipitable anxiety are designated +; those without are designated —; the total for the whole group is designated T. In the ensuing description of the groups, I shall not refer to the presence or absence of anxiety elicited by injection of epinephrine, but shall refer merely to the blood pressure reaction pattern characteristic for each of the seven major groups (Fig. 1).

Group I. Epinephrine: Moderate or marked rise of blood pressure.

Mecholyl: Marked, moderate, or slight, but prolonged rise of systolic blood pressure above the preinjection level, sometimes after a very brief and slight fall, the blood pressure remaining or fluctuating above the preinjection level for the major part of the 25-minute observation period (Fig. 1*A* and *B*).

Group II. Epinephrine: Marked rise of systolic blood pressure.

Mecholyl: Moderate or slight fall of systolic blood pressure, followed by an early temporary rise above the preinjection level, but with establishment of homeostasis, i. e.,

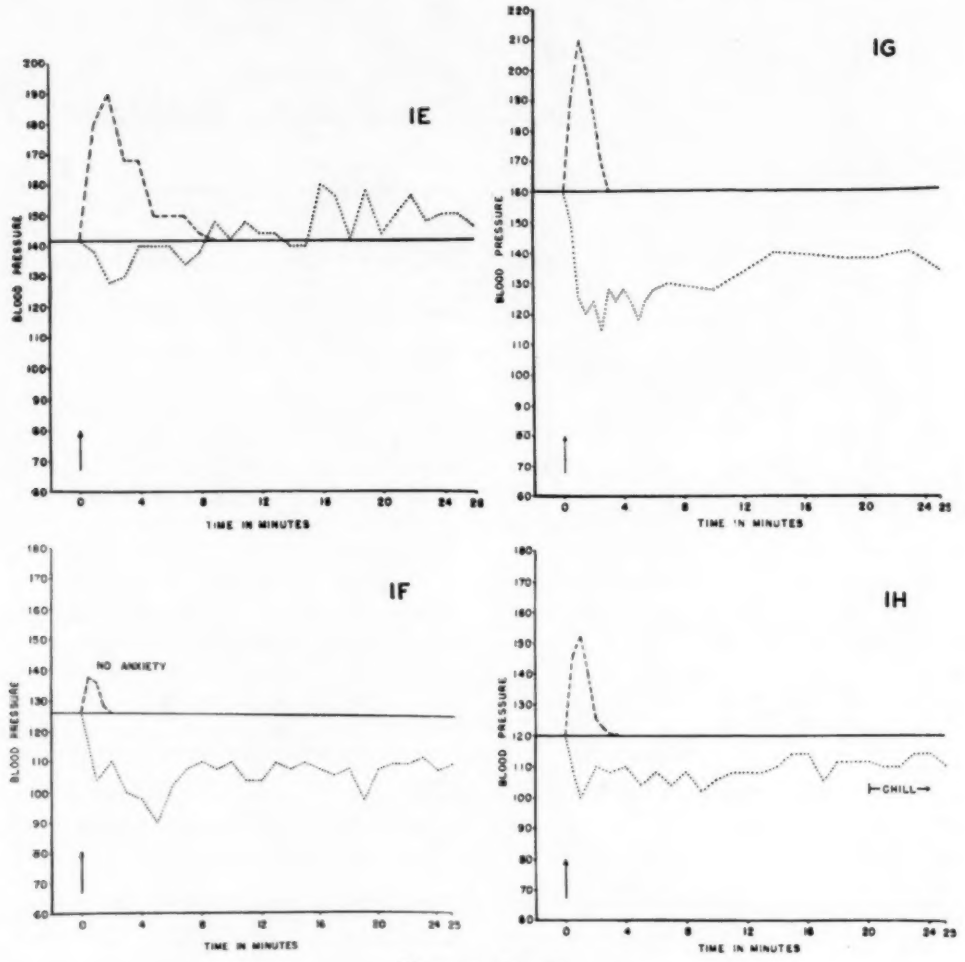

Figure 1—E to H

return to the preinjection level of the blood pressure, usually within the first 8-10 minutes, and maintenance of it throughout most of the remainder of the 25-minute observation period (Fig. 1*C*).

Group III. Epinephrine: Moderate or marked rise of systolic blood pressure.

Mecholyl: Moderate or slight fall in systolic blood pressure, without rise above the preinjection level, but with homeostasis, i. e., return to the preinjection level of the blood pressure, usually within the first 8-10 minutes, and maintenance of it throughout the remainder of the 25-minute observation period (Fig. 1*D*).

Group IV. Epinephrine: Moderate or marked rise of systolic blood pressure.

Mecholyl: Moderate early fall in systolic blood pressure, followed 8-10 minutes later by marked rebounding, delayed rise above the preinjection level, maintained for most of the remainder of the 25-minute observation period (Fig. 1*E*).

Group V. Epinephrine: Inadequate rise of systolic blood pressure.

Mecholyl: Moderate or marked fall in systolic blood pressure, usually, but not necessarily, with failure to return to the preinjection blood pressure level within the 25-minute observation period (Fig. 1*F*).

Group VI. Epinephrine: Moderate or marked rise of systolic blood pressure.

Mecholyl: Moderate or marked fall of systolic blood pressure, with failure to return to the preinjection blood pressure level within the 25-minute observation period (Fig. 1*G*).

Group VII. In this group all cases are included in which a chill occurred after the Mecholyl injection, in my case material in conjunction with a marked or moderate fall of the blood pressure. Although in some of these patients a reliable blood pressure curve could not be obtained owing to the noise engendered by the muscular contractions during the chill, I am of the opinion that all these patients in my material would have been classified in Group VI had it not been for the chill. This group may therefore for the most part be regarded as a special subgroup of Group VI (Fig. 1*H*).

If we examine the blood pressure reactions in these groups in terms of the adrenergic and/or cholinergic response implied, the following four general divisions can be made:

The epinephrine test allows division into two distinct groups: a large group of patients with adequate adrenergic response to the intravenous injection of epinephrine in terms of an adequate blood pressure rise (Groups I, II, III, VI, VII), and a small group, in which the adrenergic response to intravenous injection of epinephrine is inadequate (Group V).

The Mecholyl test allows division of the blood pressure reaction groups into three categories: the first, in which the reaction to Mecholyl equals that of normals not under stress (Group III); the second, in which Mecholyl has a very marked cholinergic-muscarinic effect, manifested by marked and prolonged fall of blood pressure (Groups V, VI, and VII), and a third group, in which there is a paradoxical adrenergic response to Mecholyl in that the blood pressure rises instead of falls (Groups I, II, and IV). This rise is sustained in Group I, brief and transitory in Group II, and delayed, i. e., rebounding, after a preliminary fall in Group IV. This paradoxical adrenergic effect of Mecholyl (or acetylcholine) comes about in the following manner: Acetylcholine (or Mecholyl) has both a muscarinic effect, which brings about the reactions usually classified as cholinergic, including fall of blood pressure, and a nicotinic effect, which also stimulates the ganglia of the sympathetic system, exerting an associated, although normally less marked, adrenergic effect. In the presence of excessive secretion of arterenol (norepinephrine) in the body, however, the muscarinic effect of Mecholyl is blocked (Funkenstein and associates [8]), and only its nicotinic-adrenergic effect manifests itself, thus producing a rise of the blood pressure above the preinjection level, such as occurs characteristically in Groups I, II, and IV.

We may therefore roughly define our groups as expressing various degrees of adrenergic or cholinergic response, respectively. Group I is characterized by marked adrenergic (nicotinic) response to Mecholyl; Groups VI and VII, by marked cholinergic (muscarinic) response to Mecholyl; Groups II and IV are characterized by moderate adrenergic response to Mecholyl; Group III is characterized by a response similar to that of normals not under stress, while Group V is the only group denoting any form of underresponsiveness, namely, adrenergic underresponsiveness to epinephrine. In other words, Groups I, VI, VII are the marked overreactors; Groups II and IV are moderate overreactors; Groups III is composed of the normal reactors, and Group V, of the underreactors to at least one of the test substances employed.

STATISTICAL STUDIES OF THE 201 PATIENTS

Description of Sample.—Of the 201 patients studied, 107 were cases of affective psychoses, most of them depressions; 25 had psychoneuroses, including severe phobic and obsessive-compulsive states, as well as psychoneurotic borderline conditions; 26 were suffering from schizoaffective psychoses; 43, from full-blown schizophrenia. The age and

sex distributions of the population of this study, drawn from an active private practice with emphasis on treatment of acute psychotic episodes, are comparable to those in Funkenstein's studies, which were drawn from the patients of an acute-admission hospital in an urban center. There were 64 male and 137 female patients, of ages ranging from 15 to 70 years, with an average age of 36.2 years.

The distribution of autonomic test patterns in the four diagnostic groups was as follows: In the affective psychoses, 65% fell into Groups VI and VII and 35% into Groups I to V. In the psychoneuroses, the schizoaffective psychoses, and the schizophrenic groups, the cases belonging to Groups I to V predominated, ranging from 69% to 72%, while the cases falling into Groups VI and VII ranged from 28% to 31%.

Epinephrine-precipitable anxiety was present in 46% of the affective and schizoaffective psychoses and in 56% of the psychoneuroses, the anxiety cases being about equally distributed over Groups I to V and Groups VI and VII. Only among the schizophrenics were significantly more cases with epinephrine-precipitable anxiety found in Groups VI and VII (61%) than in Groups I to V (20%), the average being 33%.

The treatments to which the patients were subjected consisted of electroshock in 112 cases, psychotherapy in 52 cases, and insulin treatment in 29 cases. Other patients were treated by such miscellaneous methods as ether drip infusion; ether abreaction, and abreaction with thiopental (Pentothal) sodium, amobarbital (Amytal) sodium, or CO_2, the individual groups being too small for separate statistical analysis. Seven patients withdrew before any treatment was initiated. However, all these patients have been included in the tabulation of "all treatments," which was aimed at the evaluation of the total recovery potential of the group. By the same token, the rare or occasional patients who had as little as one electroshock, one session of psychotherapy, or one week of insulin therapy (which was the shortest time at which a patient withdrew prematurely from this type of treatment) were included in the respective treatment groups, follow-up reports being obtained from the referring physicians. It is considered important in any kind of study of treatment results that all cases be tagged at intake and carried through the remainder of the study, because if only the patients going through the full course of treatments prescribed are considered, a selection of favorably reacting patients would result. This was scrupulously avoided in this study. The cases reported here therefore represent an entirely unselected series of all patients who consulted me with view toward treatment, and to whom I administered the Funkenstein test prior to making any recommendation for or against and/or initiating any form of treatment or management. In a few of these cases I did not subsequently administer the treatment recommended myself, because they had been referred to me by fellow psychiatrists for my opinion as to the treatment indicated. These colleagues reported the follow-up results in their patients.

The type of electroshock therapy employed consisted in a varied program utilizing both convulsive and nonconvulsive stimulation in a manner similar to the employment of these therapeutic modalities in electronarcosis (Tietz and associates [4]), as I described elsewhere (Alexander *). An average of 16 treatments (range from 1 to 63) were administered, of which an average of 5 (range from 0 to 63) were purely convulsive, an average of 1 (range from 0 to 17) was nonconvulsive, and an average of 10 (range from 0 to 31) were combined convulsive-nonconvulsive treatments. For the patients who recovered, the average number of treatments was slightly smaller, namely, 15 (range from 2 to 37 treatments) per patient. Of these, 4 (range from 0 to 28) were purely convulsive; an average of 1 (range from 0 to 8), nonconvulsive, and an average of 10 (range

* References 5 and 6.

from 0 to 31), combined convulsive-nonconvulsive treatments. The last technique is a variant of electronarcosis administered with Reiter's CW 46, CW 47, or RC 47 machine. The nonconvulsive treatments were administered with Reiter's CW 47B or 47C machine, and the convulsive treatments were administered with the Medcraft alternating current machine. In 86% of all patients treated with electroshock some form of combined convulsive-nonconvulsive technique was utilized; 12% of the patients (only 6% of the recovered group) received convulsive treatment only; 2% (of the recovered as well as of the nonrecovered group) received nonconvulsive treatment exclusively.

Psychotherapy consisted of an eclectic, dynamically oriented form of psychotherapy, administered in sessions lasting about an hour each. The number of sessions varied from 1 to 153 per patient, the average being 13. The sessions were administered at a frequency ranging from six times weekly to once every four weeks, the average being once every nine days. The total period over which psychotherapy was administered varied from 1 day to 5 years, the average being 17 weeks.

Insulin therapy consisted of full insulin coma in 21 cases, insulin subcoma only in 8. Twenty of the 29 patients treated with insulin therapy had been electroshock failures, included in the electroshock group; only 5 of them remained failures when subsequently subjected to insulin therapy. This fact alone enhances the significance of the findings regarding insulin treatment, although the total number in this group was small.

Insulin coma therapy consisted of the administration of 60-62 deep insulin comas, with the exception of two cases, in which 16 and 32 comas, respectively, sufficed to bring about recovery. The series of comas was preceded by a series of 6 to 20 subcomas, usually followed by 6 to 14 subcomas. The eight patients receiving subcomas received only an average of 15 (7-26) such treatments, gradually deepened close to coma level. All treatments were administered daily for six days during each week, every seventh day being a rest day. Six cases also were given concurrent electroshock treatments, usually after every fifth deep coma. None of these included the 20 electroshock failures who were subsequently given insulin therapy.

There was very little overlap between the group receiving psychotherapy and that receiving physical treatment. This is due to the fact that most psychotherapeutic failures in my private clinical practice who later were subjected to various forms of physical treatment could not be included in the psychotherapy group in this study because no pretreatment Funkenstein tests were carried out prior to psychotherapy. The overlap consists of only three patients. One patient who failed after two and a half years of psychotherapy subsequently recovered on electroshock therapy. This patient is carried as a failure in the psychotherapy group and as a full recovery in the electroshock group. Another patient who recovered from one of her depressions after electroshock, achieving a status of social recovery, subsequently achieved the same result with psychotherapy when her illness recurred three years later. This patient is included as a social recovery, both in the electroshock and in the psychotherapy groups. The third patient who failed on insulin coma therapy combined with electroshock subsequently achieved social recovery after two years of intensive psychotherapy. This patient is included as a failure in the insulin coma group and as a social recovery in the psychotherapy group. Apart from these three patients, there is no overlap of the psychotherapy group with the other subgroups, although psychotherapy was administered to the patients in the other groups as well, in addition to the physical modality of treatment employed.

In the "all treatments" group each patient is, of course, included only once, classified by the first Funkenstein test administered and the last treatment result obtained.

The material shall first be analyzed on the basis of the patient's initial Funkenstein test

pattern, before subdividing it by clinical diagnosis. In addition to histograms, the statistical results will be presented to classify the recovery potential inherent in all seven blood pressure reaction groups, with and without epinephrine-precipitable anxiety.

Definition of Recovery.—Funkenstein and his co-workers [1] defined their criteria for improvement as follows: A patient was considered improved if he left the hospital within a month of the last treatment and then remained out of the hospital at least one month; a patient was considered unimproved if he was not suitable for discharge from the hospital within a month without other somatic treatment, or, if discharged, he returned within the month. In my clinical work with Funkenstein's epinephrine and Mecholyl test I have attempted to study the prognostic implications of the test also in regard to two additional higher grades of improvement, namely, "full recovery" and "social recovery." For these purposes I have defined two additional grades of therapeutic result (Alexander [6]) as follows: A social remission or social recovery describes a patient who within two months after attaining the improved status, as defined above, has sufficiently improved to resume his social and occupational activities to the full, but who either has failed to achieve insight or still retains some subjective complaints or disturbances in his intimate personal life. Complete recovery denotes the restoration of the patient's mental state within two months after mere improvement, to what he and his relatives agree is his former "own best self," implying that such full recovery is associated with insight as well, although insight may not be entirely lacking in other degrees of improvement.

In this study, the recovered group is composed of the patients who have achieved either full or social recovery; the nonrecovered group is comprised of those who remained unimproved, as well as those whose improvement was only temporary or fell short of social recovery.

Statistical Methods.†—In all instances the chi-square test was used for analysis of the data. Where prediction of results was possible on the basis of previous research, one-tail tests were used. In all other cases the obtained probability value was derived from a two-tail test.

RESULTS

All Patients, All Treatments; Division by Blood Pressure Reaction Groups, by Presence or Absence of Epinephrine-Precipitable Anxiety, and by Whether or Not the Patient Recovered.—Table 1 presents the data for the seven groups with respect to recovery or nonrecovery. The results of the over-all chi-square analysis of these data indicate rejection of the null hypothesis ($P=0.03$); that is, the groups do differ with respect to frequencies of recoveries, in a statistically significant way (Table 1).

TABLE 1.—*Statistical Analysis of Cases According to Blood Pressure Reaction Grouping and Clinical Outcome for All Treatments*

Group	Recovered	Not Recovered	Recovered, %
I	6	2	75
II	15	10	60
III	17	21	45
IV	13	9	59
V	2	8	20
VI	68	28	71
VII	1	1	50

$\chi^2 = 13.87$ N = 6 $P = 0.03$

Group I differs markedly from the others in its high proportion of recovered patients, indicating that patients falling in Group I have the best prognosis. It is followed closely by Group VI in terms of favorable prognosis. Group V shows the greatest divergence from the other groups, but in a negative direction, having the lowest proportion of recoveries. This is of interest in view of the fact that Group I is comprised of patients who give the most oustanding adrenergic reactions, and Group VI, of those who give the most outstanding cholinergic (muscarinic) reac-

† Drs. Melvin Rosenthal and Irving Wolf collaborated in the statistical evaluation of the material.

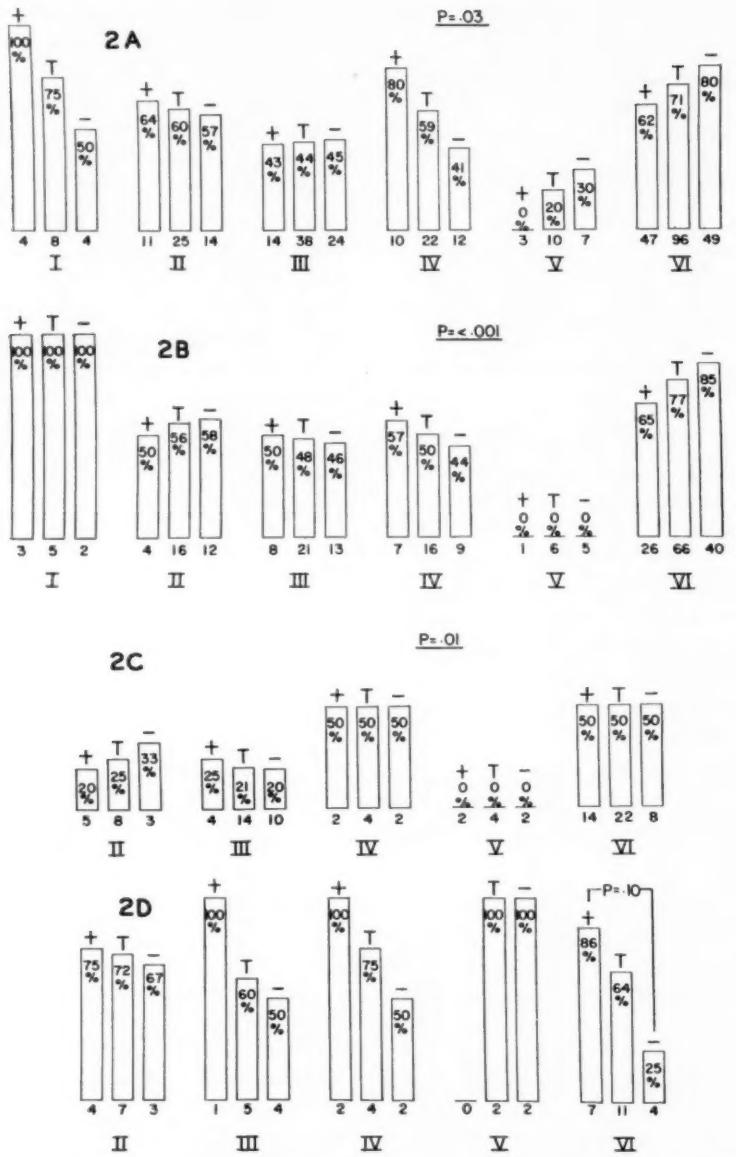

Fig. 2.—Histograms illustrating recovery rates for individual blood pressure reaction groups. One of the three histograms shown for each group represents the patients with epinephrine-precipitable anxiety (the histogram on the left, marked by +); the second represents those without epinephrine-precipitable anxiety (the histogram on the right, marked by —); the third represents the total derived from the combination of the two other groups (the histogram in the center of each group, marked by *T*). The percentage of recovered cases is shown near the top of each histogram; the total number of cases, below each histogram. The resulting recovery profiles are presented separately for the following:

A: All patients subjected to all treatments; $\chi^2=13.87$, $P=0.03$.

B: Electroshock (combined convulsive-nonconvulsive electric treatment); $\chi^2=22.74$, $P=<0.001$.

C: Psychotherapy; $\chi^2=6.23$, $P=0.01$.

D: Insulin therapy (for the latter no chi-square tests were done, owing to insufficient cases, except for anxiety (+) versus no anxiety (—) patients in Group VI: $\chi^2=1.86$, $P=0.10$).

TABLE 2.—*Chi-Square Test by Blood Pressure Reaction Grouping for All Patients, All Treatments, Testing the Relationship of Epinephrine-Precipitated Anxiety to Clinical Outcome*

Group	Relationship Based on Clinical Observation	Statistical Validation χ^2	P
I	Favorable	0.667 *	N.S.†
II	Favorable	0.007	N.S.
III	N.S.	0.032	N.S.
IV	Favorable	1.920	0.09
V	Unfavorable	3.601	0.02
VI	Unfavorable	3.716	0.02
VII	Insufficient cases		

* Yates' correction for continuity was used throughout.
† N.S. = not significant.

tions. In contrast, Group V, which responds most poorly in terms of frequency of recovery, is made up of those who show least adrenergic reactivity on the Funkenstein test. Group III, however, which is closest to the reactions of normals not under stress, is the second poorest group. Groups II and IV, which give an intermediate frequency of recovery, also exhibit an intermediate autonomic overresponsiveness, with preponderance on the adrenergic side.

Table 2 presents the chi-square analysis of the data with respect to each group and epinephrine-precipitable anxiety in relation to recovery.

The results indicate that in those patients who overreact in the cholinergic direction (such as Groups V and VI), the presence of epinephrine-precipitable anxiety is a liability, namely, a disturbing complication which interferes with treatment results. In Group IV, however, which is a group with adrenergic overreaction, there is a trend indicating that presence of epinephrine-precipitable anxiety is an asset (Table 2, Fig. 2*A*).

TABLE 3.—*Chi-Square Test Between Combined "Favorable" Versus "Unfavorable" Grouping for All Patients, All Treatments, by Clinical Outcome*

Group	Recovered	Not Recovered	Recovered, %
I-V	53	50	52
VI-VII	69	29	70

$\chi^2 = 7.561$ $N = 1$ $P = < 0.01$

All Patients, All Treatments; Division by Combined "Favorable" and "Unfavorable" Groups.—Table 3 presents the results obtained by comparing groups described as prognostically favorable by Funkenstein and co-workers (Groups VI and VII) with those he considered unfavorable (I through V).

Comparison of the frequency of recovery in these two combined groups in the population of this study gives results similar to Funkenstein's; that is, Groups VI and VII had a significantly greater proportion of recoveries (70%) than Groups I through V (52%) ($P<0.01$; Table 3, Fig. 3).

When the relationship between the presence of epinephrine-precipitable anxiety and

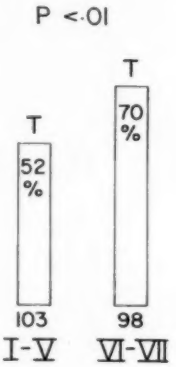

Fig. 3.—Recovery rate for all patients grouped into "unfavorable" (*I-V*) and "favorable" (*VI* and *VII*) group combinations ($P = <0.01$).

subsequent recovery is examined for each group, it is found that in Groups VI and VII the probability that absence of epinephrine-precipitable anxiety will be a therapeutic asset is very high ($P=0.01$; Table 4, Fig. 4). In Groups I to V, however, only a trend appears indicating that epinephrine-precipitable anxiety may be prognostically favorable ($P=0.10$; Table 4, Fig. 5).

All Patients, All Treatments; Division by Groups of Adrenergic and Cholinergic Overreaction.—Because of the fact that the presence or absence of epinephrine-precipitable anxiety appeared to influence the treatment results divergently when the groups were combined into the "favorable" and "unfavor-

TABLE 4.—*Chi-Square Test for Groups I-V ("Unfavorable") and VI-VII ("Favorable") Combination, for All Patients, All Treatments, Testing the Relationship of Epinephrine-Precipitated Anxiety to Clinical Outcome*

Group	Relationship Based on Clinical Observation	Statistical Validation	
		χ^2	P
I-V	Presence favorable	1.848	0.10
VI-VII	Absence favorable	4.508	0.01

able" classifications, a different division appeared promising, made on the basis of the physiologic characteristics of the autonomic nervous system response to the Funkenstein test, namely, to separate the adrenergic overreactors (Groups I, II, IV) from the cholinergic overreactors (Groups V, VI, VII), excluding Group III (whose autonomic pattern is similar to that of normals not under stress).

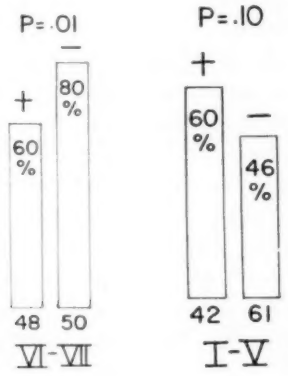

Figure 4

Figure 5

Fig. 4.—Recovery rates of patients in Groups VI and VII classified by presence (+) and absence (—) of epinephrine-precipitable anxiety. Note that the absence of epinephrine-precipitable anxiety is a therapeutic asset ($P = 0.01$).

Fig. 5.—Recovery rates of patients in Groups I to V, subdivided into those with (+) and those without (—) epinephrine-precipitable anxiety. Note trend that epinephrine-precipitable anxiety may be a prognostic asset in this group (P=0.10).

TABLE 5.—*Chi-Square Test Between Adrenergic (I, II, IV) and Cholinergic Overreactors (V-VII) for All Patients, All Treatments by Clinical Outcome*

Group	Recovered	Not Recovered	Recovered, %
I, II, IV	34	21	62
V-VII	71	37	66

$\chi^2 = 0.245$ N = 1 P = N.S.

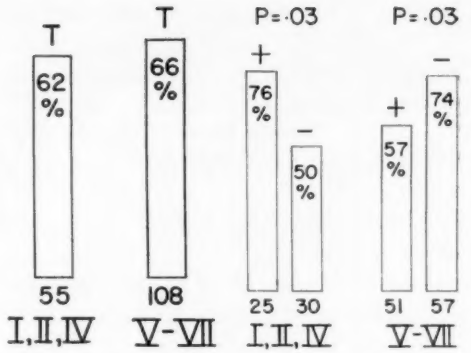

Figure 6 Figure 7

Fig. 6.—Recovery rates of patients in groups defined as adrenergic overreactors (*I, II, IV*) compared with those defined as cholinergic overreactors (*V-VII*). Note that recovery rates in these two major group combinations are statistically not different from each other (62% *vs.* 66%).

Fig. 7.—Histograms illustrating the prognostic effect of epinephrine-precipitable anxiety (+) in the adrenergic overreactors (*I, II, IV*) and in the cholinergic overreactors (*V-VII*). Note that epinephrine-precipitable anxiety (+) is prognostically favorable in the adrenergic overreactors, while absence of epinephrine-precipitable anxiety (—) is prognostically favorable in the cholinergic overreactors ($P = 0.03$).

When the recovery rates of these two new major group combinations were compared, as indicated in Table 5, there was no significant difference between them (Fig. 6). Thus, when the data are reordered according to autonomic reaction and that group which is closest to normal is eliminated, the results indicate that adrenergic overreactivity is equally as favorable a prognostic sign as cholinergic overreaction. Cholinergic over-

TABLE 6.—*Chi-Square Test for Groups I, II, IV and Groups V-VII, Testing the Relationship of Epinephrine-Precipitated Anxiety to Clinical Outcome*

Group	Relationship Based on Clinical Observation	Statistical Validation	
		χ^2	P
I, II, IV	Favorable	3.906	0.03
V-VII	Unfavorable	3.382	0.03

reaction had made a more favorable showing in Funkenstein's [1] earlier grouping because it was in contrast with a mixed group containing not only the adrenergic overreactors (I, II, IV) but the normal reactors (III) and the adrenergic underreactors (V) as well.

A further breakdown of the data, taking only Groups I, II, and IV in relation to proportion of recovered cases, indicates that epinephrine-precipitable anxiety is a favorable factor in the adrenergic overreactors (P=0.03); in contrast, epinephrine-precipitable anxiety is a liability in the cholinergic overreactors (Groups V, VI, VII) (P=0.03; Table 6, Fig. 7).

The fact that patients with epinephrine-precipitable anxiety do better if they fall in Groups I, II, or IV may possibly be explained by the assumption that measures likely to relieve adrenergic overreactivity are also likely to relieve epinephrine-precipitable anxiety, while the reverse is true for cholinergic overreactivity.

Patients Treated by Electroshock; Division by Blood Pressure Reaction Groups, by Presence or Absence of Epinephrine-Precipitable Anxiety, and by Clinical Outcome.—The chi-square over-all test for differences between the groups was highly significant (P<0.001; Table 7, Fig. 2B). It can be seen that recovery rates were high (67%-100%) in Groups I, VI, and VII, and intermediate (48%-56%) in Groups II, III, IV, while on the side of poor prognosis

TABLE 7.—*Statistical Analysis of Cases According to Blood Pressure Reaction Grouping and Clinical Outcome for Electroshock Therapy (Combined Convulsive-Nonconvulsive Treatment)*

Group	Recovered	Not Recovered	Recovered, %
I	5	0	100
II	9	7	56
III	10	11	48
IV	8	8	50
V	0	6	0
VI	51	15	77
VII	2	1	67

$\chi^2 = 22.742$ N = 6 $P = < 0.001$

TABLE 8.—*Chi-Square Test Between "Favorable" (VI-VII) Versus "Unfavorable" (I-V) Combined Groups for Patients Treated with Electroshock (Combined Convulsive-Nonconvulsive Treatment), Classified by Clinical Outcome*

Group	Recovered	Not Recovered	Recovered, %
I-V	32	32	50
VI-VII	53	16	77

$\chi^2 = 10.348$ N = 1 $P = < 0.001$

Group V was outstanding, with no recoveries. The most reliable percentage of recoveries is that shown by Group VI, containing the greatest number of cases. However, the fact that all cases in Group I recovered, while in Group V none recovered, would seem to indicate a meaningful trend in spite of the small number of cases.

Analysis of the data with respect to frequency of recoveries in each group in relation to presence or absence of epinephrine-precipitable anxiety revealed that the absence of epinephrine-precipitable anxiety was an asset in Group VI (Fig. 8) (χ =4.66, P=0.02). The χ^2 values were nonsignificant for the role of epinephrine-precipitable anxiety in the individual groups II, III, and IV; the lack of sufficient number

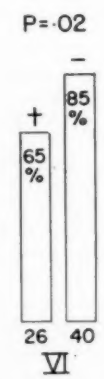

Fig. 8.—Recovery rate of 66 patients in Group VI treated by electroshock (combined convulsive-nonconvulsive treatment) divided into those with (+) and those without (—) epinephrine-precipitable anxiety. Note that the recovery rate is higher in the group free from epinephrine-precipitable anxiety (χ^2=4.66, P=0.02).

of cases precluded statistical analysis of these data.

Patients Treated by Electroshock; Division by Combined Groups, by Presence or Absence of Epinephrine-Precipitable Anxiety, and by Clinical Outcome.—A breakdown by "favorable" versus "unfavorable" groups according to Funkenstein's designation showed that the difference in the proportion of recoveries between the two groups was highly significant ($P<0.001$) in the expected direction, supporting his findings (Fig. 9, Table 8).

In Groups I to V there was no significant difference in frequency of recovery between those with and those without epinephrine-precipitable anxiety (Table 9, Figs. 10*B* and 11). In Groups VI and VII, however, absence of epinephrine-precipitable anxiety is an asset ($P=0.02$; Table 9, Figs. 10*B* and 12).

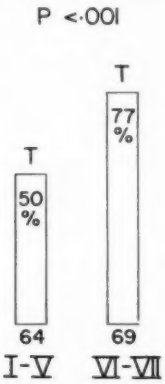

Fig. 9.—The recovery rate of patients treated with electroshock (combined convulsive-nonconvulsive treatment) in Groups I to V contrasted with that in Groups VI and VII. Note that the recovery rate is significantly higher in Groups VI and VII, designated as "favorable" by Funkenstein (77% *vs.* 50%; $\chi^2=10.35$, $P=<0.001$).

TABLE 9.—*Chi-Square Test for Groups I-V and VI-VII for All Patients Treated with Electroshock (Combined Convulsive-Nonconvulsive Treatment), Testing the Relationship of Epinephrine-Precipitated Anxiety to Clinical Outcome*

Group	Relationship Based on Clinical Observation	Statistical Validation χ^2	P
I-V	Favorable	0.061	N.S.
VI-VII	Unfavorable	4.776	0.02

TABLE 10.—*Chi-Square Test for Combined Groups, I, II, IV, and V-VII for All Patients Treated with Electroshock (Combined Convulsive-Nonconvulsive Treatment), Testing the Relationship of Epinephrine-Precipitated Anxiety to Clinical Outcome*

Group	Relationship Based on Clinical Observation	Statistical Validation χ^2	P
I, II, IV	Favorable	0.006	N.S.
V-VII	Unfavorable	2.135	0.05

The only difference between the findings of the present study and that of Funkenstein and his co-workers with respect to electroshock therapy is the much greater frequency of recovery in the "unfavorable" groups (I-V) with epinephrine-precipitable anxiety in my case material, 56% (Fig. 13), as against his 11.8% (Funkenstein and associates ‡), whereas the recovery rate of patients with epinephrine-precipitable anxiety in the "favorable" groups was identical (63% in my material versus 62.5% in the case material of Funkenstein and associates[1]) (Fig. 13). This difference in findings may be due to a difference in treatment techniques. In the present study a varied program utilizing both convulsive and nonconvulsive stimulation was administered, mostly in the form of combined convulsive-nonconvulsive treatments (modified electronarcosis). Purely nonconvulsive treatments were administered particularly when disturbing anxiety erupted during treatment. All of Funkenstein's patients, on the other hand, received convulsive treatment exclusively. It thus would appear that the combined convulsive-nonconvulsive treatment technique benefits those patients in the "unfavorable" groups (I-V) who exhibit epinephrine-precipitable anxiety. This also indicates that the old classification "favorable-unfavorable" appears limited to response to convulsive electroshock as far as this group is concerned; on the basis of the present data it would appear that the distinction no longer discriminated between their two subgroups with epinephrine-precipitable anxiety.

‡ Funkenstein and others,[1] Fig. 5, p. 356.

When the incidence of recovery in cholinergic overreactors (V-VII) was compared with that of adrenergic overreactors (I, II, IV), no statistically significant difference was found between the groups (χ^2=1.41)—perhaps due to the liberal use of nonconvulsive treatment.

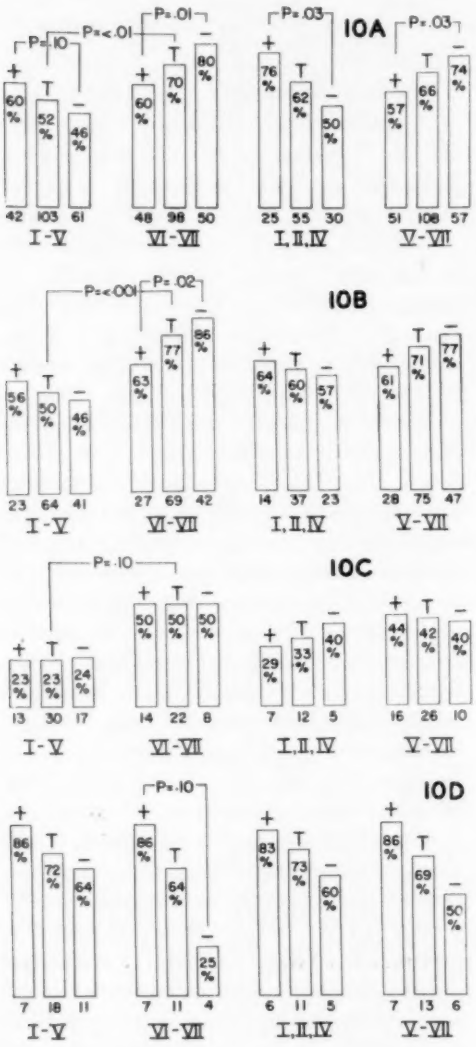

Fig. 10.—Histograms of recovery rates by group combinations.

A: For all patients and all treatments.

B: For patients treated with electroshock (combined convulsive-nonconvulsive electric treatment).

C: For patients treated with psychotherapy.

D: For patients treated with insulin therapy.

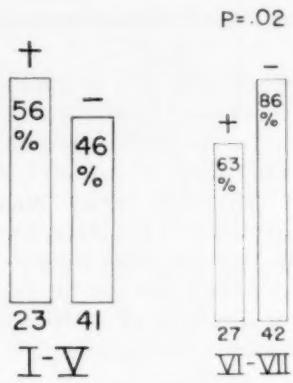

Figure 11

Figure 12

Fig. 11.—Recovery rates after electroshock (combined convulsive-nonconvulsive treatment). Patients with epinephrine-precipitable anxiety (+) are compared with those without epinephrine-precipitable anxiety (—), in Groups I to V. Note absence of significant difference between the two groups.

Fig. 12.—Recovery rates after electroshock (combined convulsive-nonconvulsive treatment). Patients with epinephrine-precipitable anxiety (+) are compared with those without epinephrine-precipitable anxiety (—) in Groups VI and VII. Note that absence of epinephrine-precipitable anxiety is an asset in this group combination (86% *vs.* 63%, χ^2=4.776, P=0.02). (Compare Funkenstein and associates,[1] Fig. 6, p. 357.)

The presence of epinephrine-precipitable anxiety did not appear to influence the recovery rate in Groups I, II, and IV (adrenergic

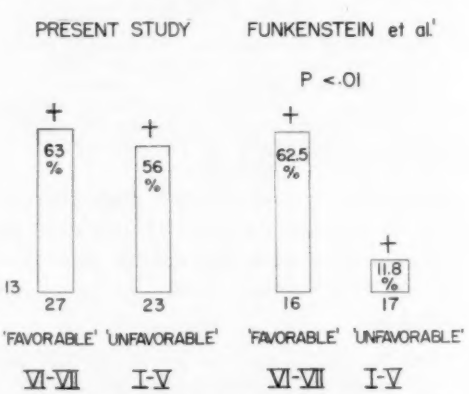

Fig. 13.—Comparison of the recovery rates after electroshock therapy in the present study and in Funkenstein's case material, for all patients with epinephrine-precipitable anxiety, divided into "favorable" (*VI* and *VII*) and "unfavorable" (*I-V*) groups. Note that while the recovery rate in the "favorable" group is identical in the two patient populations, the recovery rate in the "unfavorable" group is higher in the present study, probably due to the added use of nonconvulsive treatment in my case material.

overreactors) (Table 10, Fig. 10*B*). In Groups V to VII (cholinergic overreactors), absence of epinephrine-precipitable anxiety is an asset (P=0.05; Table 10, Fig. 10*B*).

PSYCHOTHERAPY

When an overall test was done to see whether any differences existed between the blood pressure reaction groups in their response to psychotherapy, that is, in the frequencies of recovery among the different groups, the chi-square test demonstrated such a difference between groups at a statistically significant level (P=0.01; Table 11, Fig. 2*C*).

TABLE 11.—*Statistical Analysis of Cases According to Blood Pressure Reaction Grouping and Clinical Outcome for Psychotherapy*

Group	Recovered	Not Recovered	Recovered, %
I	No cases treated		
II	2	6	25
III	3	11	21
IV	2	2	50
V	0	4	0
VI	11	11	50
VII	No cases treated		

$\chi^2 = 6.232$ $N = 3$ $P = 0.01$

Tests of the groups individually suggest that anxiety does not influence the outcome of psychotherapy one way or the other.

When the groups receiving psychotherapy are combined into Funkenstein's "favorable" and "unfavorable" groups, recovery rates were 50% in the favorable groups (VI-VII) and 23% in the unfavorable groups (Fig. 10*C*). The chi-square test, however, discriminates between the two groups only at the trend level (χ^2=2.74, P=0.1). Analysis of the difference between groups combined on the basis of autonomic reactivity showed no significant difference between the two groups (33% for Groups I, II, and IV, 42% for Groups V-VII) (Fig. 10*C*).

Epinephrine-precipitable anxiety within all four classifications did not influence the treatment results.

INSULIN THERAPY

Because of the small number of patients who were given insulin treatment (29 cases), full statistical analysis was not feasible, except for Group VI. In this group it was found that those patients with epinephrine-precipitable anxiety tended to benefit from insulin treatment more than those free from epinephrine-precipitable anxiety (Figs. 2*D* and 14). Statistically this was a trend only (χ^2=1.86, P=0.1). The statistically demonstrated trend is consistent with the clinical impression that epinephrine-precipitable anxiety is a favorable prognostic indicator for insulin treatment generally (Fig. 10*D*).

It should be noted that the only Group V patients in the present series who recovered were the two patients treated by insulin therapy (Fig. 2*D*, compare Fig. 2*B* and *C*).

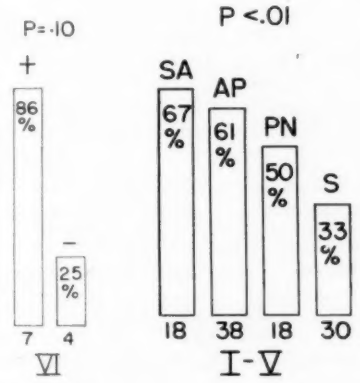

Figure 14

Figure 15

Fig. 14.—Recovery rate after insulin therapy of patients in Group VI divided into those with (+) and those without (—) epinephrine-precipitable anxiety. Note trend (P=0.10) indicating epinephrine-precipitable anxiety as a favorable prognostic item for insulin therapy.

Fig. 15.—Recovery rates for patients in the "unfavorable" blood pressure reaction groups (*I-V*) divided by clinical diagnosis. *SA*=schizoaffective psychoses; *AP*=affective psychoses; *PN*=psychoneuroses; *S*=schizophrenia. Note that recovery rates in these four clinical diagnostic groups are significantly different from each other (P=<0.01).

Both these patients had been electroshock failures (after 44 and 13 treatments, respectively); both achieved full recovery after 60 deep insulin coma treatments.

All Patients, All Treatments; Division by Clinical Diagnosis, Combined Blood Pressure Reaction Groups, Presence of Epinephrine-Precipitable Anxiety, and Clinical Out-

come.—When our cases were divided by diagnosis, by "favorable" versus "unfavorable" grouping (Groups I-V versus VI-VII), and by the presence or absence of epinephrine-precipitable anxiety, the following statistically significant facts emerge: In Groups I-V, the outcome is significantly determined by clinical diagnosis; patients with affective psychoses and schizoaffective psychoses do best (61% and 67% recovered respectively); psychoneurotics next (50%), and schizophrenics (33%) last. The differences in these diagnostic groups are significant at less (better) than the 0.01 level (Table 12, Fig. 15).

In contrast to the behavior of the diagnostic groups in categories I-V, the clinical diagnostic groupings in blood pressure reaction Groups VI-VII do not contribute significantly to determination of outcome. The rates for improvement are 73% for affective psychoses, 75% for schizoaffective psychoses, 62% for schizophrenia, and 57% for psychoneurosis. Differences among these groups were statistically nonsignificant (Fig. 16).

TABLE 12.—*Statistical Analysis for Combined Blood Pressure Reaction Groups I-V, for All Treatments, Classified by Clinical Diagnosis and by Clinical Outcome*

Clinical Diagnosis	Recovered	Not Recovered	Recovered, %
Affective psychosis	23	15	61
Psychoneurosis	9	9	50
Schizoaffective psychosis	12	6	67
Schizophrenia	10	20	33

$\chi^2 = 6.86$ N = 3 $P = < 0.01$

In the affective psychoses, those falling into the autonomic Groups VI-VII show a higher rate of recovery (73%) than those falling into Groups I-V (61%). This difference merely indicates a trend at the 0.10 level of significance. In the schizophrenias the recovery rate in Groups I-V was 33%, as compared with 62% in Groups VI-VII (Figs. 15 and 16). This difference is significant at the trend level only (P=0.08). In the psychoneuroses and schizoaffective psychoses, the differences in the recovery rates between Groups I-V, on the one hand, and VI-VII, on the other, were not significant. In the schizoaffective psychoses the figure was 67% for Groups I-V and 75% for Groups VI-VII. In the psychoneuroses, the figure was 50% for Groups I-V and 57% for Groups VI-VII.

These findings demonstrate that the addition of the clinical diagnosis to the classification of autonomic pattern does not improve, or detract from, the clinical recovery rate in Groups VI-VII. However, the addition of the clinical diagnosis in Groups I-V enhances the prediction as to clinical outcome (Table 12).

The presence of epinephrine-precipitable anxiety does not significantly affect the outcome in Groups I-V irrespective of diagnostic category. However, in Groups VI-VII, epinephrine-precipitable anxiety affects the outcome adversely in the affective psychoses, but only at the 0.04 level of confidence.

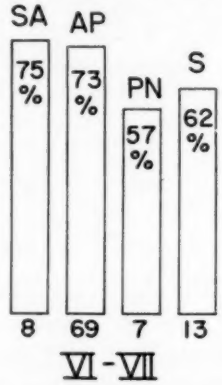

Fig. 16.—Recovery rates for patients in the "favorable" blood pressure reaction groups (*VI* and *VII*) divided by clinical diagnosis. *SA*=schizoaffective psychoses; *AP*=affective psychoses; *PN*=psychoneuroses; *S*=schizophrenia. Recovery rates in these four clinical diagnostic groups do not differ significantly from each other.

The difference in the recovery rate between patients suffering from affective psychoses (61%) and schizophrenia (33%) respectively, belonging to blood pressure reaction Groups I-V, is statistically significant at the 0.02 level (χ^2=4.96). The difference in the recovery rate between patients suffering from affective psychoses (73%)

and schizophrenia (62%) belonging to blood pressure reaction Groups VI-VII is not statistically significant.

COMMENT

In reviewing the results of the prognostic significance of blood pressure reaction grouping without reference to the presence or absence of epinephrine-precipitable anxiety, it is found that with respect to clinical outcome—after all forms of treatment—our patients fall into four prognostic groups (Fig. 2*A*). The best prognostic groups with recovery rates from 71%-75% are Groups I and VI. These are the two groups in whom one of the autonomic responses most markedly exceeds those of normals not under stress—in the adrenergic direction in Group I, in the cholinergic direction in Group VI. The second best recovery rate is obtained in Groups II and IV, with about 60% recoveries. These are the two groups in which there is only a moderate adrenergic overreaction to Mecholyl—in Group II also to epinephrine. The recovery rate in patients of Group III—whose autonomic responses most closely resemble those of normals not under stress—is 44%. The only truly unfavorable recovery rate, 20%, was obtained in Group V, which is the only group whose adrenergic response to intravenous injection of epinephrine is below par. The fact thus emerges that recovery appears to be generally correlated to the degree to which the autonomic responses of the patient differ from those of normal persons not under stress, the rates being correspondingly high when autonomic responsiveness is greater than normal, and low when one of the autonomic responses falls below normal, while the recovery rate of those patients whose autonomic responses most closely resemble those of normals not under stress is about intermediate.

The prognostic role of epinephrine-precipitable anxiety varies among the groups most strikingly when they are arranged in two group combinations composed of the adrenergic overreactors, on the one hand (Groups I, II, and IV), and the cholinergic overreactors (Groups V, VI and VII), on the other hand (Fig. 10*A*). It is shown that epinephrine-precipitable anxiety is a favorable prognostic item in the adrenergic overreactors, while freedom from epinephrine-precipitable anxiety is a favorable prognostic item in the cholinergic overreactors.

The profile of the recovery potential of patients treated with electroshock—of which I employed a varied combined convulsive-nonconvulsive technique classifiable as modified electronarcosis—shows sharper differentiation in some respects but appears leveled off in others, in comparison with the profile of the over-all recovery potential of all groups (compare Figs. 2*A* and 10*A* with Figs. 2*B* and 10*B*). The most striking item of sharper differentiation is the fact that Group V patients have a still more unfavorable prognosis when subjected to electroshock only, none of the patients in this group having attained recovered status after electroshock therapy. On the other end of the scale, Groups I and VI emerge as even more favorable prognostically if only the patients subjected to electroshock are considered. The recovery rates in Groups II, III, and IV, however, have leveled off at about 50%. Furthermore, the prognostically favorable element of epinephrine-precipitable anxiety among the adrenergic overreactors (Groups I, II, and IV; Fig. 10*B*) has become eliminated. This indicates that electroshock —even the combined convulsive-nonconvulsive variant which I employ—is not as effective for the relief of anxiety as the combination of all treatments. Nevertheless, it is shown by my material that the combined convulsive-nonconvulsive form of treatment which I employed has succeeded in eliminating the particularly adverse effect of epinephrine-precipitable anxiety in the group combination classified as "unfavorable" by Funkenstein and associates,[1] namely Groups I-V. Funkenstein and associates [1] had found that of the patients with epinephrine-precipitable anxiety in this combined group (I-V) whom they had treated with purely convulsive electroshock, only 11.8% recovered, whereas I found that in this group—if

treated with combined convulsive-nonconvulsive electroshock—56% recovered (Figs. 10*B* and 13).

In the "favorable" group combination (VI-VII), however, the addition of nonconvulsive treatment to the electroshock regimen did not enhance the recovery rate. It was 63% for the patients with epinephrine-precipitable anxiety in that group combination for my patients treated with combined convulsive-nonconvulsive treatment, and 62.5% for Funkenstein's corresponding cases treated with convulsive electroshock only (Fig. 13). It would seem, therefore, that the addition of nonconvulsive treatment was beneficial to the group hitherto considered prognostically "unfavorable," namely, for the patients in Groups I-V with epinephrine-precipitable anxiety, while it did not seem to increase the recovery rate of patients with epinephrine-precipitable anxiety in the "favorable" groups, VI and VII. This difference in the effect of nonconvulsive treatment in these two groups may be due to the fact that relief of anxiety was of more crucial importance in the "unfavorable" groups (I-V), in which anxiety and its derivatives were frequently the major clinical problem, while in the "favorable" groups, in which depression and related regressive psychotic manifestations constituted the outstanding disability, relief from anxiety was a merely incidental benefit, which did not affect the recovery rate per se. The relief of anxiety in these cases, nevertheless, was clinically beneficial, effecting the smooth management of the patient and shortening his period of illness, a fact which fails to be adequately reflected in the ultimate recovery rates computed. A significant example may be given here.

A 40-year-old patient, suffering from a severe depression, was found to have blood pressure reactions characteristic of Group VI, with epinephrine-precipitable anxiety. She was treated with 12 combined convulsive-nonconvulsive electroshock treatments. Improvement proceeded uneventfully; anxiety and/or aversion to treatment remained absent. Her recovery was complete in eight weeks. By contrast, her identical twin sister, who was given a series of 12 purely convulsive electroshock treatments in other hands, had to struggle through a period of agitated post-treatment turmoil, culminating in early relapse of severe depression, this time complicated with marked anxious agitation, requiring another series of 10 to 12 electroshock treatments, after which she began to recover slowly, her period of disabling illness extending over seven months. While these identical twin sisters both recovered ultimately, the addition of nonconvulsive treatment definitely eased the treatment and shortened the illness period for the one receiving combined convulsive-nonconvulsive treatment.

If we now review the way in which the epinephrine-Mecholyl test reflects the recovery potential of the patients when subjected to psychotherapy, two groups appear to be outstanding, namely, Groups IV and VI, with recovery rates of 50% each. The recovery rates in Groups II and III are low (25% and 21%), while none of the patients in Group V who were subjected to psychotherapy recovered (Fig. 2*C*). It is of interest that Group VI, with its high recovery rate after electroshock therapy, also has a relatively high recovery potential with psychotherapy. The significant advantage of electroshock therapy in this group (VI) is not so much that an average of 77% of the patients achieve recovery but that 27% can be expected to achieve recovery over and above the 50% who can be counted on to recover on a regimen of psychotherapeutic measures alone.

The situation is different in Group IV. Here the recovery rate for psychotherapy is equal to that with electroshock. In other words, electroshock does not add to the ultimate recovery potential of the patients in Group IV. Electroshock is therefore not indicated in this Group except as a symptomatic measure for the relief of severe depressive turmoil. However, the relief afforded by electroshock to patients falling in Group IV is only transitory, and relapses are frequent unless the patient makes progress on

concurrent psychotherapy, the patient's ultimate recovery depending upon the psychotherapeutic work achieved with him.

The presence or absence of epinephrine-precipitable anxiety does not significantly influence the results achieved with psychotherapy.

The most interesting finding concerning the influence of insulin therapy upon the recovery potential of the various autonomic reaction groups is the consistent trend favoring patients with epinephrine-precipitable anxiety. The conclusion is justified that insulin is the treatment of choice for those patients in whose clinical symptomatology epinephrine-precipitable anxiety plays a marked role.

The fact that the only two patients in Group V who recovered were the two treated with insulin coma therapy may be a point of departure for further research on this interesting group of patients.

In comparing the predictive value of autonomic reaction pattern and the clinical psychiatric diagnosis, we find that in the most favorable, as well as in the most unfavorable, blood pressure reaction groups the predictive value of the test exceeds the predictive value of clinical diagnosis. This was statistically proved in the combined Group VI-VII. The recovery rate was uniformly high in this blood pressure reaction group, irrespective of psychiatric diagnostic category, differences in recovery rate among the four clinical psychiatric diagnoses represented as subgroups being statistically insignificant. In other words, if a patient belongs to blood pressure reaction Groups VI-VII, his recovery potential is determined by this fact, irrespective of whether he is suffering from an affective, schizoaffective, or schizophrenic psychosis, or from a psychoneurosis.

By contrast, in the "unfavorable" combined Group I-V, the recovery potential was determined significantly by the clinical diagnosis at less (i. e., better) than the 0.01 level of confidence. Unfortunately, the numbers were too small to determine the trends concerning the prognostic value of clinical diagnosis in the individual primary groups composing this combined Group I-V, although it appears on inspection of the data that Groups II, III, and IV are the groups in which clinical psychiatric diagnosis has the greatest bearing upon outcome, since in Group I the recovery rates were uniformly high and in Group V generally low.

SUMMARY

Statistical study of 201 consecutive patients confirms the basic thesis proposed by Funkenstein and associates [1] that prognostic implications can be derived from the epinephrine-Mecholyl test.

The recovery potential of the patients is shown to be positively correlated with the intensity of the autonomic responses elicited. The recovery potential is high in patients with a greatly enhanced response to Mecholyl, either in cholinergic-muscarinic or in adrenergic-nicotinic direction, slightly less in patients with a moderately enhanced response, low in patients in whom one of the responses (that to epinephrine) is below par, and intermediate in those patients whose autonomic responses do not significantly differ from those of normals not under stress.

Absence of epinephrine-precipitable anxiety is prognostically favorable in cholinergic (muscarinic) overreactors, while presence of epinephrine-precipitable anxiety is prognostically favorable in the adrenergic (nicotinic) overreactors.

To electroshock therapy—of which a combined convulsive-nonconvulsive variant was employed similar to the combination of these modalities in electronarcosis—the most marked cholinergic and adrenergic overreactors responded best. Of the patients whose response to epinephrine was inadequate, none recovered with electroshock and/or psychotherapy, electroshock, as well as psychotherapy, being entirely ineffective in that group (Group V). The only Group V patients who achieved recovery were the two patients treated with insulin coma.

Epinephrine-precipitable anxiety nowhere represented a prognostically favorable item for response to electroshock therapy; however, it was less of a liability in our patients

receiving combined convulsive-nonconvulsive treatment than in the patients treated with purely convulsive electroshock reported by Funkenstein and associates.[1] In the combined Groups I-V, epinephrine-precipitable anxiety was thus eliminated as a liability altogether; the recovery rate of the patients with combined convulsive-nonconvulsive treatment (modified electronarcosis) was about equal for the subgroup with and for the subgroup without epinephrine-precipitable anxiety.

For Group IV, the recovery rate with psychotherapy was equal to that with electroshock therapy. Electroshock should therefore not be administered to Group IV patients except for purely symptomatic relief and should not be counted on to contribute to the ultimate recovery of the patient. This appears to depend upon the success of the psychotherapeutic work with the patient.

Epinephrine-precipitable anxiety is a prognostically favorable item for patients undergoing insulin therapy.

In the most favorable and the most unfavorable blood pressure reaction groups the predictive value of the epinephrine-Mecholyl test exceeds the predictive value of clinical diagnosis.

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Subcortical Connections from Temporal Cortex of Monkey

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The neocortex of the lateral surface of the temporal lobe of man and monkey may be divided cytoarchitecturally into three main portions: temporal tip (TG), superior temporal gyrus (TA), and second temporal gyrus (TE).* As these areas have been shown to possess important functions,† it is obviously desirable to determine, as precisely as possible, their connections with the remainder of the brain.

Earlier studies have revealed pathways connecting the temporal cortex with portions of the thalamus and lower brain stem.‡ The present experiments have employed electrical recording and neuronographic techniques to investigate temporal connections with the basal ganglia, the amygdala, and the neighboring rhinencephalic cortex.

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† Adey, W. R.; Segundo, J. P., and Livingston, R. B.: Cortical Influences on Brain Stem Conduction, in preparation.

References 4, 7, 8, 16, 26, and 30.

Segundo, J. P.; Arana, R., and French, J. D.: Behavioral Arousal upon Cortical Stimulation in Normally Sleeping Monkeys, in preparation.

‡ References 1, 2, 4, 5, 11, 17, 21, 27, 28, 29, and 32.

MATERIALS AND METHODS

Nineteen monkeys (Macacus mulattus) were prepared under ether anesthesia, immobilized by the intravenous injection of tubocurarine chloride U. S. P. (*d*-tubocurarine), and maintained under artificial respiration. The temporal cortex was exposed by a small craniotomy and protected by the application of warm liquid petrolatum U. S. P. at regular intervals. Pairs of silver-ball-tipped electrodes, 2 mm. apart, were used to stimulate or record from the cortex. Bipolar concentric electrodes, made of Stainless Steel and oriented stereotactically, were employed for recording from the interior of the brain, and placements were checked histologically. The portions of the brain that were explored are indicated in Figure 1 by stippling. Activity was recorded with an ink writer and, when necessary, with a cathode ray oscilloscope.

The connections of each of the cortical areas mentioned were investigated, using the following procedures: 1. Strychnine neuronography. A 1-sq.-mm. piece of filter paper impregnated with a saturated solution of strychnine sulfate was applied to the cortex until adequate local spiking occurred. 2. Evoked potentials. Single square-wave pulses of 0.1- to 1-msec. duration were applied to the cortex through a stimulus isolation unit. So as to reduce the artifact as much as possible, durations of 0.1 msec. were used preferentially; even under these conditions, intensities below 15 volts were sufficient to evoke the responses described below. The effect of the repetition of these stimuli at frequencies up to 50 cps were also tested regularly. 3. Localized after-discharge. Localized after-discharge (detected by recording electrodes placed in the immediate vicinity of the excited cortex) was induced by a stimulus of adequate voltage and standardized values of pulse duration (1 msec.), frequency (50 cps), and total duration (2 seconds) and its propagation to deep structures recorded.

The positive and the negative results obtained with each technique were recorded on the corresponding maps of frontal sections of each monkey's brain. No contralateral effects were analyzed.

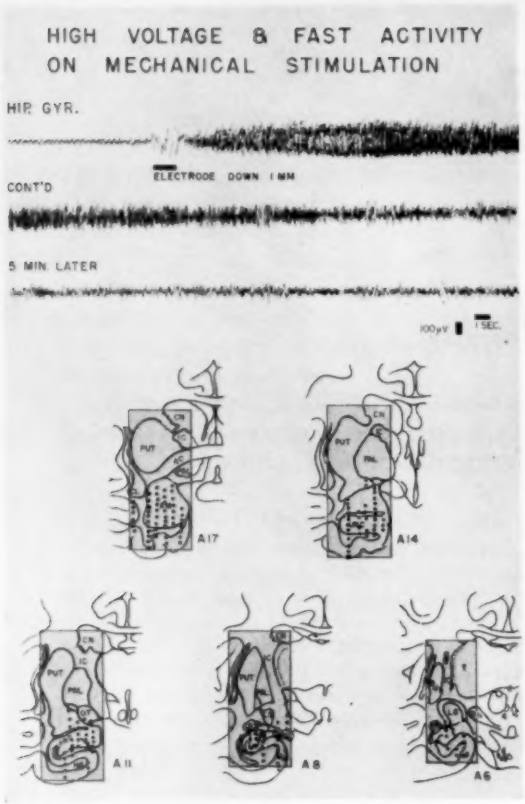

Fig. 1.—Above: electroencephalographic tracing from hippocampal gyrus. Moving the electrode down 1 mm. induces high voltage and fast activity. Below: frontal sections of the monkey brain. Stippling shows areas explored in these experiments. Black dots show points exhibiting, on arrival of the electrode, a high voltage and fast activity. Abbreviations: *AC*, anterior commissure; *AM*, amygdala; *CL*, claustrum; *CN*, caudate nucleus; *HIP GYR*, *HG*, hippocampal gyrus; *IC*, internal capsule; *LG*, lateral geniculate; *OT*, optic tract; *PAL*, globus pallidus; *PUT*, putamen; *SN*, substantia nigra; *T*, thalamus; *UNC*, uncus.

RESULTS

The spontaneous EEG encountered in certain subcortical areas exhibited features which distinguished it rather notably from that found elsewhere (black dots, Fig. 1). When the electrode tip was lowered into one of these points, the record immediately displayed typical high-voltage (up to 300μv), fast activity (30-60 cps), which would increase in intensity for a few seconds and, during the next five minutes, wane to a less characteristic lower voltage and slower rhythm (Fig. 1). Points showing this fast activity were situated in the rhinencephalon (amygdala, hippocampus proper, and hippocampal gyrus) or were located in its immediate vicinity (cortex of the sulcus temporalis superior, lower portion of the putamen, optic tract, tail of the caudate nucleus, pes pedunculi, and lateral geniculate body).

The propagation of the different induced disturbances may be summarized with refer-

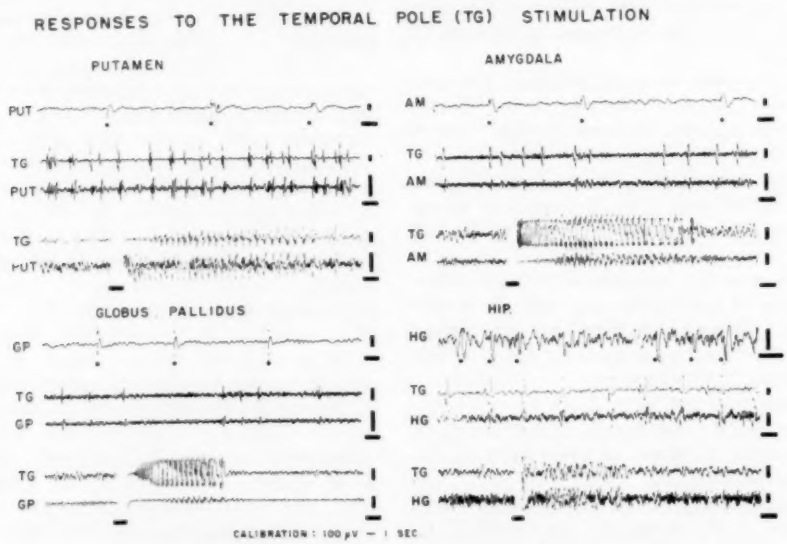

Fig. 2.—Electroencephalographic tracings showing responses to different forms of temporal pole stimulation: evoked potentials (top tracing of each group); strychnine (middle two tracings); after-discharge (lower two tracings). Abbreviations: *AM*, amygdala; *GP*, globus pallidus; *HIP*, *HG*, hippocampal formation; *PUT*, putamen; *TG*, temporal pole.

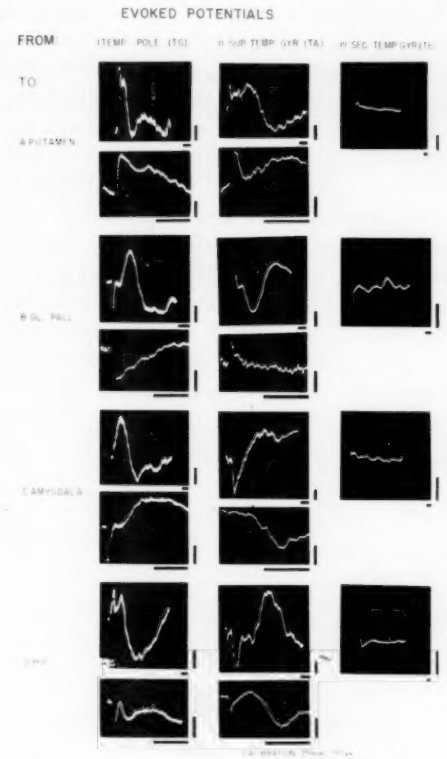

Fig. 3.—CRO tracings of evoked potentials resulting from stimulation of the following structures: temporal pole (left-hand verical column), superior temporal gyrus (middle vertical column), or second temporal gyrus (right-hand vertical column), in putamen (top and second horizontal lines), globus pallidus (third and fourth horizontal lines), amygdala (fifth and sixth horizontal lines), and hippocampal formation (seventh and bottom horizontal lines). Recordings in horizontal lines 2, 4, 6, and 8 were made with a faster sweep so as to detect earlier responses. Abbreviations: *GL PALL*, globus pallidum; *HIP*, hippocampal formation; *SEC TEMP GYR (TE)*, second temporal gyrus; *SUP TEMP GYR (TA)*, superior temporal gyrus; *TEMP POLE (TG)*, temporal pole.

ence to component areas of the temporal cortex excited as follows:

A. Stimulation of Temporal Tip (TG) (Figs. 2, 3, 4, and 5).—1. Strychnine Spikes: Strychnine spikes were recorded in the putamen, globus pallidus, anterior commissure, amygdala, hippocampus proper, hippocampal gyrus, and buried cortex of the sulcus temporalis superior. When some time had elapsed since the placement of the strychnine solution and the cortical spikes were weaker as a result, the local spiking could be abolished completely by high-frequency stimulation of the amygdala (2-7 volts, 1 msec., 100 cps). This observation is similar to one described by Feindel and Gloor,[9] who used a non-saturated solution of the drug. It was not possible to obtain this effect when the spikes from TG were at their peak.

2. Evoked Potentials: Evoked potentials were recorded in the putamen, globus pallidus, amygdala, hippocampus proper, and hippocampal gyrus, as well as in the anterior commissure, nucleus basalis, pes pedunculi, lateral geniculate, and nucleus reticularis thalami. Responses evoked by temporal pole excitation usually consisted of an initial wave of moderate amplitude followed by a higher voltage and more prolonged deflection (Fig. 3). Minor oscillations occasionally followed, and when the probing electrodes were in the head of the caudate nucleus, the globus pallidus, or the reticular nucleus of the thalamus, these latter waves amounted to actual 9-16 cps spindles, very similar to those appearing spontaneously.

The initial phase of the evoked discharge was usually visible in the putamen, globus pallidus, amygdala, hippocampus proper, and hippocampal gyrus from 7 to 20 msec. after the stimulus. Occasionally, however, latencies were even shorter, and the response started directly after the stimulus artifact. The succeeding major deflection, on the other hand, appeared around 30 msec. after the stimulus and lasted for as long as 150 msec. When repetitive excitation was applied, it was observed that responses evoked in the lenticular nucleus were reduced with frequencies over 4 cps, while potentials evoked in the amygdala, hippocampus proper, and hippocampal gyrus not only followed stimulation impulses up to 15 cps but were enhanced optimally and regularly with values of 4-8 cps (Fig. 4). This enhancement was maximal from the beginning and did not exhibit "augmentation" or "recruitment."

3. After-Discharge: After-discharge, when elicited locally in the temporal cortex from threshold stimulation, did not result in sub-

cortical propagation. A more prolonged discharge was transmitted to the putamen, globus pallidus (medial portion), amygdala, hippocampus proper, hippocampal gyrus, and buried cortex of the sulcus temporalis superior. It seemed that, after a prolonged experiment, the rhinencephalic structures, and especially the amygdala, became more responsive to temporal pole excitation. Under such circumstances, the amygdaloid after-discharge could be induced more easily, occurring as a result of small temporal seizures, or even after stimulation not followed by a detectable after-discharge in TG. Once started, the subcortical alteration would proceed with an entirely independent frequency and outlive the primary phenomenon (Fig. 5). In one such instance, simple mechanical stimulation of the temporal tip was sufficient to induce an amygdaloid seizure.

2. Evoked Potentials: Evoked potentials were elicited in the putamen, globus pallidus, amygdala, hippocapus proper, hippocampal gyrus, internal capsule, anterior commissure, nucleus basalis, head of caudate nucleus, and reticular nucleus of thalamus (Fig. 3). These responses exhibited an early deflection of small amplitude followed by a major wave and, when recorded in the caudate nucleus, putamen, or globus pallidus, triggered 9-16 cps bursts (Fig. 4). They differed, however, from potentials evoked from TG in that they presented a somewhat slower time course, characterized by longer latencies of 8-15 msec. for the first wave and up to 100 msec. for the major deflection. The early response might not appear in the globus pallidus. "Recruitment" or "augmentation" was exhibited in the responses of the caudate nucleus, putamen, globus pallidus, and reticular nucleus of the thalamus induced by low-frequency (4-8 cps) stimulation of TA. In these nuclei, the amplitude of the main wave increased for the first three or four shocks; later it decreased, or even disappeared, and, throughout a prolonged stimulation, waxed and waned periodically (Fig. 4). By con-

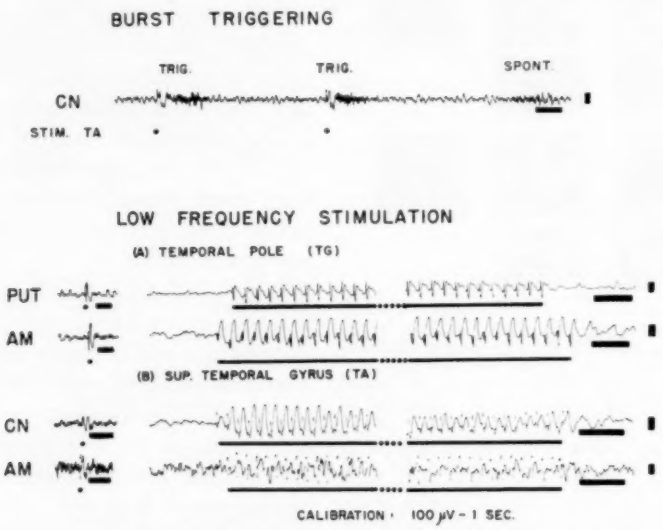

Fig. 4.—Electroencephalographic tracings. Above: triggering of bursts in caudate nucleus by stimulation of superior temporal gyrus. Below: effect of low-frequency stimulation of temporal pole and of superior temporal gyrus in gray nuclei and in rhinencephalic structures. Abbreviations: *AM*, amygdala; *CN*, caudate nucleus; *PUT*, putamen; *STIM*, stimulation; *SPONT*, spontaneous; *SUP*, superior; *TA*, superior temporal gyrus; *TG*, temporal pole; *TRIG*, triggered.

B. Stimulation of Superior Temporal Gyrus (TA) (Figs. 3, 4, 6).—1. Strychnine Spikes: Strychnine spikes were recorded in the putamen, globus pallidus, lateral portion of the amygdala, hippocampal gyrus, hippocampus proper, and anterior commissure.

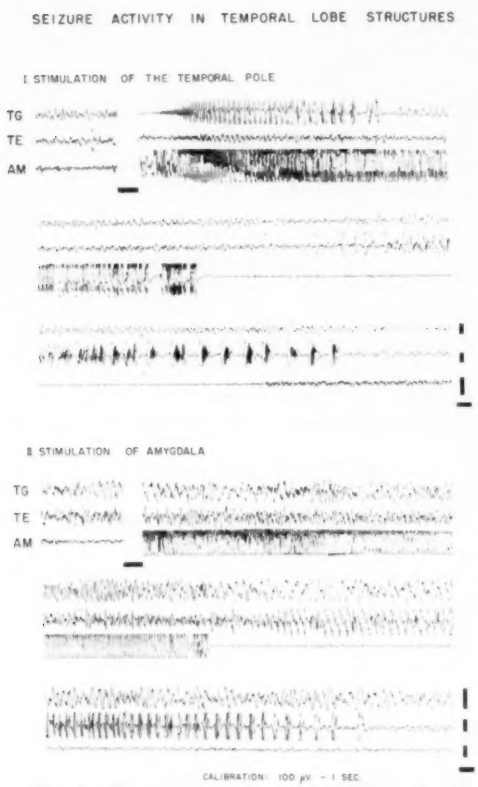

Fig. 5.—Electroencephalographic tracing of seizure activity in temporal lobe structures when "spontaneous" spikes occurred in the second temporal gyrus. *I*, on stimulation of temporal pole; *II*, on stimulation of amygdala. Abbreviations: *AM*, amygdala; *TE*, second temporal gyrus; *TG*, temporal pole.

trast, the rhinencephalic responses to 4-8 cps stimulation was not as prominent as in the single shocks.

3. After-Discharge: In most cases, the after-discharge induced in TA led to a concomitant and similar effect in TG, this being especially true for the most anterior portions of the superior temporal gyrus. This seizure would also reach most of the subcortical areas involved upon primary excitation of TG. By careful selection of the voltages, it was possible to obtain in the superior temporal gyrus an after-discharge not propagated to the tip. Under these circumstances subcortical transmission was usually poor; occasionally, however, a similar activity would be recorded from the putamen, the globus pallidus, the amygdala, the hippocampus proper, the hippocampal gyrus, and the internal capsule. After-discharges from the more posterior portion of TA had a certain tendency to propagate to TE.

C. Stimulation of Second Temporal Gyrus (TE) (Figs. 3, 7).—Stimulation of the second temporal gyrus with all of the methods employed resulted in the propagation of no clear-cut responses except for an occasional strychnine spike in the globus pallidus. In spite of every precaution, this region very frequently showed, after a prolonged experiment, "spontaneous" spikes of irregular frequency which lacked an obvious propagation to the subcortical electrodes. No information exists as to the cause of these spikes or as to the reason for their preferential localization. An after-discharge in the amygdala, whether induced by its direct stimulation or propagated from TG, very commonly abolished such spikes in TE, or at least reduced their frequency. The cessation of the deep disturbance would then be consistently followed by a marked and transitory increase in the epileptoid manifestations of TE (Fig. 5). These sporadic observations exhibit a certain similitude with clinical reports of Gastaut and associates § in which a first seizure initiated in a focus on one temporal tip is followed, after it has died out, by a second discharge in the homolateral posterior temporal and occipital areas.

It may be added here that, occasionally, one or more of the methods applied for detecting corticosubcortical connections exhibited, in different experiments, apparently conflicting results. We cannot offer an explanation for this behavior but consider the positive results described, and especially those related to the putamen, globus pallidus, amygdala, hippocampus proper, and hippocampal gyrus, as significant. No definite relationship could be found between the distribution of evoked responses in the amygdala and the nuclear configuration of that structure.

COMMENT

The high-voltage fast activity apparently induced simply by shifting the tip of the

§ References 13 and 14.

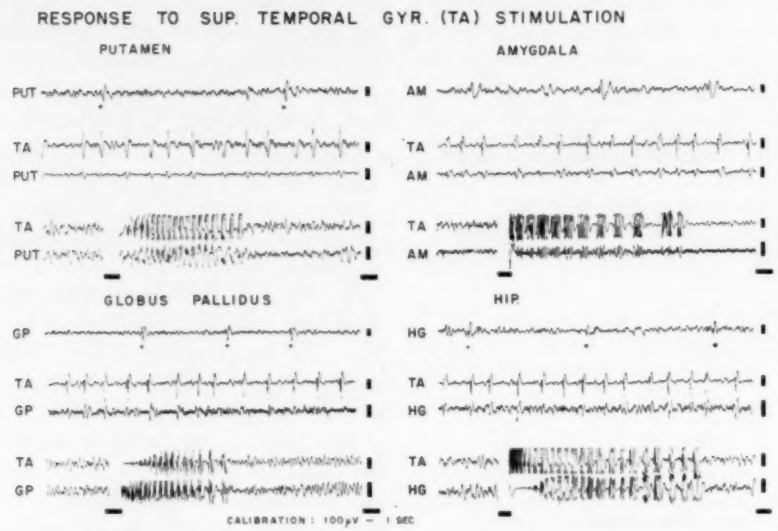

Fig. 6.—Electroencephalographic tracings showing response to different forms of superior temporal gyrus stimulation: evoked potentials (top tracing of each group); strychnine (middle two tracings); after-discharge (lower two tracings). Abbreviations: *AM*, amygdala; *GP*, globus pallidus; *GYR*, gyrus; *HIP*, *HG*, hippocampal formation; *PUT*, putamen; *SUP*, superior; *TA*, superior temporal gyrus.

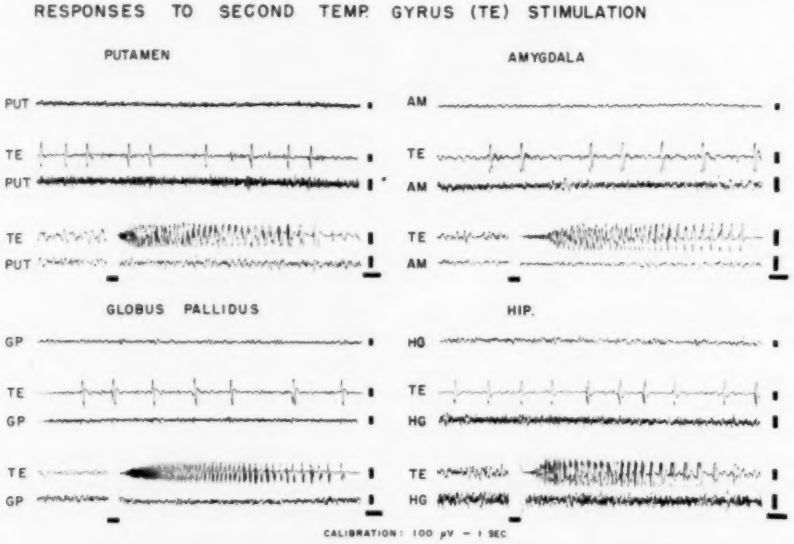

Fig. 7.—Electroencephalographic tracings showing responses to different forms of second temporal gyrus stimulation: evoked potentials (top tracing of each group); strychnine (middle two tracings); after-discharge (lower two tracings). Abbreviations: *AM*, amygdala; *GP*, globus pallidus; *HIP*, *HG*, hippocampal formation; *PUT*, putamen; *TE*, second temporal gyrus; *TEMP*, temporal.

electrode within the rhinencephalon constitutes a finding familiar to workers in the field. The marked susceptibility of these structures to mechanical stimulation would agree with the findings of Gastaut,[12] Kaada,[19] and Morin and Green [22] of a low threshold for seizure induction upon electrical stimulation. It is difficult to establish the exact nature of this pattern of induced electrical activity; the high voltage would suggest some type of epileptic activation, but its gradual fading out differs from the abrupt cessation of a more genuine after-discharge. In one instance only did the high-voltage fast activity increase and merge into a typical seizure pattern. The term "injury discharge" has been applied to this activity by others.

In regard to the main results, the present experiments, confirming and extending previous communications,‖ show that there exists the possibility of a preferential transmission of strychnine spikes, evoked potentials, and epileptic activity from the temporal tip and superior temporal gyrus to important subcortical structures, such as the lenticular nuclei, the hippocampus proper, the hippocampal gyrus, and the amygdala. Though the exact topography of the different routes of transmission can hardly be surmised from the information collected here, some pertinent general considerations may be inferred. The brief latencies shown by potentials evoked from the temporal tip (TG) in the lenticular nucleus, and especially in the rhinencephalic structures, together with the propagation of strychnine spikes to these regions, favor the hypothesis that these neural influences may be mediated through paucisynaptic chains or even direct pathways. Unless it is proposed that the initial fast volley induces a local excitation responsible for the major late wave, the rapidly conducting route would appear to be complemented by devious or multisynaptic chains also coursing from TG to the subcortical structures mentioned. A somewhat similar consideration may be advanced in reference to the superior temporal gyrus (TA), if it is kept in mind that, in general, latencies from this portion of the cortex to the rhinencephalon were somewhat longer and that the early responses were infrequent in the globus pallidus.

As judged by the effect of low-frequency stimulation, it would seem that certain further differences exist, however, between the corticifugal projections from TG and TA. Whereas the lenticular response to excitation of TG deteriorated at a frequency of 8 cps, the evoked potentials in the rhinencephalic gray matter were enhanced. In contrast, stimulation of the TA at this frequency had unfavorable effects on responses in the amygdala and hippocampal formation; the caudate, lenticular and reticular nuclei, on the other hand, reacted optimally in a fashion that has certain similarities with the recruiting response of Dempsey and Morison.[6]

The relationship between the superior temporal gyrus and the temporal tip is a most intimate one. Corticocortical connections have been demonstrated by previous workers [27] and seemingly subserve the propagation of even small after-discharges from TA to TG. Furthermore, the subcortical distribution of responses evoked from each one of these areas has shown an obvious overlap.

The second temporal gyrus, on the other hand, exhibits a very different picture, for practically no projections were found to the lenticular or rhinencephalic structures explored in these experiments. Such contrasting results suggest the possibility that the sulcus temporalis superior may separate cortical areas of different functional significance, and this suggestion is supported also by other observations.¶ A closer analysis of the functions and connections of the second temporal gyrus would seem to be of interest.

It is now generally recognized that structures in the temporal lobe play a fundamental role in the pathogenesis of psychomotor

‖ References 1, 2, 4, 5, 11, 17, 21, 27, 28, 29, and 32.

¶ References 4, 7, 8, 16, 26, 30. Adey, W. R.; Segundo, J. B., and Livingstone, R. B.: Cortical Influences on Brain Stem Conduction, in preparation.

Segundo, J. B.; Arana, R., and French, J. D.: Behavioral Arousal upon Cortical Stimulation in Normally Sleeping Monkeys, in preparation.

epilepsy #; recently, Gastaut [13] has proposed that the cortex in the vicinity of the temporal pole, diencephalic structures, or the amygdala-hippocampus may be responsible in different instances, the last structures being affected more frequently. The similarity of certain basic manifestations exhibited in all types of psychomotor fits suggests that these disturbances may arise from disorders of a common anatomical area, presumably the amygdala and the hippocampal gyrus.*

Data from these experiments would support these views. Certainly the disturbance might arise within the rhinencephalic structures themselves, as indicated by their propensity to exhibit abnormal and at times confined discharge upon mechanical or electrical stimulation. Equally tenable is the possibility that the discharge originates in a cortical focus in the temporal pole of the superior temporal gyrus, areas which have been demonstrated to connect intimately with the amygdala-hippocampus. It would seem possible, then, for the basic manifestations of psychomotor disorders to arise as the result of a seizure that commenced primarily in rhinencephalic areas or that was propagated secondarily to them through connections from the lateral temporal cortex.

While certain common phenomena displayed by patients with psychomotor seizures, e. g., automatic activity, may perhaps be assigned basically to the aforementioned rhinencephalic structures, dissimilarities in the manifestations of the disorder may pertain to alternative or associated pathways shown to exist. Connections of the temporal neocortex with the basal ganglia and of these structures and the amygdala with diffusely projecting portions of the thalamus, hypothalamus, and midbrain † would seem to present an anatomical substrate for variations in behavior of patients with psychomotor epilepsy.

It has been observed in these experiments that, under certain conditions, an after-discharge in the amygdala (secondary to one in the temporal pole, or primary) may course and persist independently of what is happening at the cortical level. This reinforces the well-known principle that a normal EEG does not necessarily signify normal activity in the entire brain. Furthermore, it suggests caution in the use of the word "postictal" when applied to certain phenomena (alteration in consciousness, etc.) appearing late in the course of a seizure when the EEG is normal or nearly so. These manifestations could well be genuinely ictal in the sense that they may be the direct consequence of deep seizure activity that cannot be detected by the usual clinical routine.

In general, it may be said that previous studies in the fields of experimental and clinical neurophysiology have attributed to the portions of the temporal lobe studied in this work a variety of more or less complex functions involving the somatic, autonomic, and intellectual spheres.‡ There can be no doubt that a correct interpretation of the physiology of these regions, as that of any other part of the brain, will be subordinated to a better knowledge of their efferent and afferent connections.

SUMMARY

Connections from different parts of the temporal lobe to the basal ganglia, amygdala, and rhinencephalic cortex have been studied in the monkey by strychnine neuronography, evoked potential, and propagated seizure techniques. A preferential propagation was found from the temporal pole (TG) and from the superior temporal gyrus (TA) to the homolateral putamen, globus pallidus, amyg-

References 10, 13, 18, 20, 23, 24, and 25. Kaada, B. R.: Temporal Lobe Seizures, read at the Third International Congress of Electroencephalography and Clinical Neurophysiology, Cambridge, Mass., Aug. 16-21, 1953.

* References 13, 20, 25, and 33. Kaada, B. R.: Temporal Lobe Seizures, read at the Third International Congress of Electroencephalography and Clinical Neurophysiology, Cambridge, Mass., Aug. 16-21, 1953.

† References 9, 15, 17, and 31.

‡ References 4, 7, 8, 16, 26, and 30. Segundo, J. P.; Arana, R., and French, J. D.: Behavioral Arousal upon Cortical Stimulation in Normally Sleeping Monkeys, in preparation.

dala, hippocampus proper, and hippocampal gyrus. Little or no propagation of activity to these structures was manifested upon stimulation of the second temporal gyrus (TE).

The findings indicate close functional relationships between the tip and the superior gyrus of the temporal lobe, and suggest a fundamentally different mode of organization of connections, and hence of function, of the second temporal gyrus.

Abundant and relatively direct connections from the tip and superior temporal gyrus to subcortical and rhinencephalic structures may help to clarify the role of these cortical areas in somatic, autonomic, and psychic spheres.

The facile propagation of seizure discharge initiated in the temporal tip and superior temporal gyrus to the amygdala may support recent proposals for an equivalent potentiality of both temporal cortex and amygdala in the genesis of psychomotor types of epilepsy. The present observation that evoked afterdischarge is transmitted with equal facility to the putamen and globus pallidus raises the question of whether the basal ganglia, together with the amygdala, may participate in seizure activity during a psychomotor fit.

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Nature of Certain Osseous Lesions in Tuberous Sclerosis

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It has been well established that characteristic roentgenographic signs may play a significant part in the diagnosis of the syndrome known as tuberous sclerosis. Recently, Holt and I [1] demonstrated that 66% of our patients had definite roentgenographic changes in the phalanges of the hands and feet. A similar incidence has since been found by Berland.[2] We pointed out that the histologic nature of these lesions had not been demonstrated, but speculated that "the bone cysts are not cysts at all in the true sense of the word. They probably represent areas of nonspecific fibrous replacement similar to that found in the transient cortical defects of growing tubular bones and certain cystic forms of neurofibromatosis of bone."

This report is concerned with the histologic structure of the lesions found in the terminal phalanges of the hands of a patient suffering from tuberous sclerosis.

REPORT OF A CASE

J. O., a white woman of Polish descent, was admitted to the Caro State Hospital for Epileptics on Oct. 22, 1930. At that time she was 18 years of age. The history indicated that she was born following a normal pregnancy and natural delivery. She cried a great deal during early infancy, but otherwise her early development was within normal limits. She had a convulsive seizure at 1½ years, and a second at 5. They recurred regularly from that time. She completed the sixth grade in public school at the age of 13, when she was excluded because of her frequent epileptic attacks. Before admission, she was stubborn, ill-tempered, and incorrigible and, on two occasions, made abortive attempts at suicide.

Examination at the time of admission showed an acne-like eruption on the face and a plaque, not otherwise described, on the forehead. Otherwise, no unusual findings were recorded. Examination in 1938 showed the patient to be obviously mentally deficient, confused, and disoriented. There were many raised, pinkish to light-brown lesions in butterfly distribution over the cheeks, nose, and chin, resembling adenoma sebaceum. There were five raised, light-brown, nontender papules on the forehead, ranging in size from 0.4 to 1 cm. Over the occiput was a 4×4×1 cm., soft, movable, nontender mass. The skin of the back showed many scattered, slightly raised, light-pink, nontender, soft lesions. The remainder of the examination was within normal limits. There were no abnormalities in the reflexes or in the sensory examination and no significant toe signs. Biopsy of one of the papules on the face returned a diagnosis of adenoma sebaceum. The fibrotic lesion on the scalp was removed; the histologic diagnosis was "tuberous sclerosis with active degeneration of hair shafts and small cystic areas forming in the sebaceous glands, extending into the hair shafts, together with an outstanding sclerosis and hyalinization of stroma." Roentgenograms of the skull showed numerous calcified plaques, either in the calvaria or on the surfaces of the cerebral hemisphere. A pneumoencephalogram showed normal-size ventricles without midline shift or distortion. In the PA view, there were seen calcified plaques in the region of the third ventricle, and a nodule projecting into the atrium of the left lateral ventricle. A repeat pneumoencephalogram in 1940 showed essentially the same findings. Intravenous pyelograms were interpreted as showing minimal distortion of the kidney pelves; the kidney outlines could not be distinguished. Roentgenograms of the hands showed cystic dilatations in the tips of the terminal phalanges of all fingers. Films of the feet showed wavy periosteal changes in the metatarsals. Several electroencephalographic examinations were made. The last, which was done Oct. 11, 1950, is summarized as follows: "This strikingly abnormal study is highly indicative of focal brain damage in the right temporal area. There is ex-

From the Caro State Hospital for Epileptics.

Dr. Orville T. Bailey did a great amount of work in the study of this material.

Read at the 30th Annual Meeting of the Central Neuropsychiatric Association, Detroit, Oct. 8, 1954.

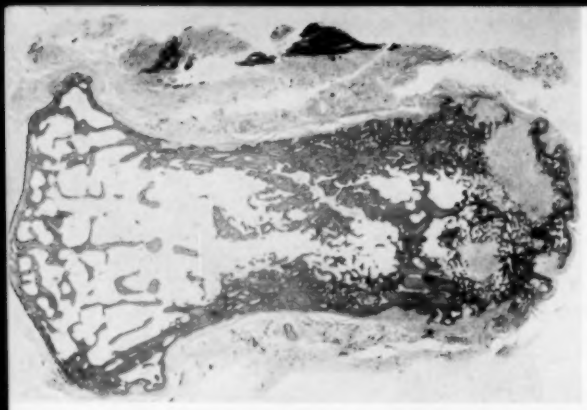


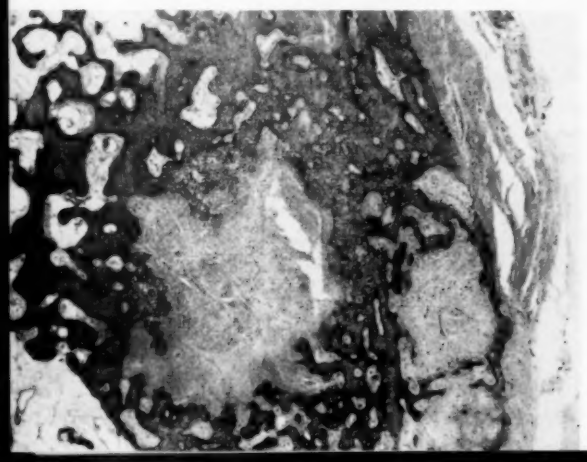
Fig. 1.—Low-power photomicrograph of the distal phalanx of the right index finger showing areas of fibrous replacement of bone identified in roentgenograms as "cysts."

tension into the frontal pole. The pattern shown is associated with local atrophic disturbance and also suggestive of grand mal and petit mal epilepsy. The patient had a previous EEG on Aug. 21, 1946, which showed the right temporal focus, but the basic pattern cannot be compared with today's study, as the recording amplifications and techniques vary. The patient appears to be highly resistive to drug sedation."

The patient's course in the hospital was characterized by recurring periods of violence, both toward other patients and toward employees. She required almost constant seclusion except that she was allowed out-of-doors alone in the day yard one or two hours daily when weather permitted. Adequate seizure control was never achieved in spite of numerous changes in medication. She died suddenly in a seizure on June 3, 1952.

At autopsy, the extensive adenoma sebaceum over the face and the brownish elevated plaques on the forehead were noted. There was deformity of the nail beds on all of the fingers of both hands. The heart and lungs showed no unusual findings other than extensive pulmonary edema. The spleen was approximately twice normal size, weighing 350 gm.

Fig. 2.—Areas of fibrous tissue from distal phalanx of right ring finger corresponding to the cyst-like areas in roentgenograms. These areas are composed of tightly packed, fully mature collagenous tissue containing no bone or osteoid. There is no suggestion of neurofibromatosis or other neoplastic lesion.



The kidneys were approximately five times normal size, the right weighing 600 and the left 750 gm.; almost all of the normal kidney tissue had been replaced by tumor formation. Before the brain was shipped to the neuropathological laboratory, roentgenograms were obtained, after fixation. In addition to the calcifications in the region of the third and lateral ventricles, there was demonstrated an area of calcification in the region of the dentate nuclei of the cerebellum; this area had not been demonstrated in roentgenograms taken during life. A roentgenogram of the calvaria at the time of autopsy demonstrated the presence of sclerotic plaques, as seen in previous cases. The terminal phalanges of the eight fingers were removed. Sections of other organs, the brain, eyes, kidneys, and terminal phalanges of the right hand were sent to Dr. Orville Bailey, Carter Memorial Hospital, Indianapolis. The terminal phalanges of the left hand were sent to Dr. Carl V. Weller, Professor of Pathology at the University of Michigan Medical School. The report on the material submitted to Dr. Weller was as follows:

"Terminal Phalanges of Left Hand: The specimens from the phalanges can be described together. They show areas of lack of bone in various stages of fibrous replacement. Dense collagenous connective tissue mingled with adipose tissue is found in these defects. Neighboring cortical and cancellous bone is thickened with added layers of new bone, giving a pattern which is much like that found in Paget's disease. There is a complete lack of osteoplastic activity; so the picture is entirely different from that found in most of the other bone conditions in which bone destruction is occurring actively. These defects appear to be of long standing and to be undergoing partial repair rather than enlargement."

The report from Dr. Bailey on the material submitted to him is as follows:

"Brain: The brain was cut in coronal sections at intervals of 1 cm. On examination of the gross sections, many localized nodules were found scattered through the cerebral cortex and in the periventricular regions. There was also a single nodule in the dentate nucleus of the cerebellum, extending into adjacent folia. This measured 0.7 cm. in diameter.

"Microscopic sections were prepared from many areas and stained with hematoxylin-eosin, Mallory's phosphotungstic acid-hematoxylin, and Sudan black. These showed the typical lesions of tuberous sclerosis. The nodules consisted of large cells with long, thick processes embedded in a network of glial cells, elongate cells, and occasional nerve cells. The tubers in the periventricular regions and in the cerebellum contained extensive areas of calcification, usually deposited in relation to blood vessels of capillary size. Lesions nearer the surface of the

brain did not contain calcium deposits. Sections of the pons, medulla, and spinal cord presented no evidence of abnormality.

"Eyes: There was some scarring of the external limiting membrane, but no clear-cut phacoma was present.

"Kidneys: Both kidneys were extensively distorted and partially replaced by large tumors, which were clearly separated from the parenchyma, but which did not have well-defined capsules. Histologically, each tumor was composed of a mixture of tissue types, including fat tissue, collagenous connective tissue, smooth muscle fibers, and a few tubular structures. All tissue elements were well differentiated and there were no areas of anaplasia or intense cellularity.

"Other Viscera: Microscopic sections of liver, adrenal, heart, and spleen revealed no evidence of tumor or other abnormality. There was evidence of an organized pneumonia in sections of the lungs.

"Phalanges: Material from four terminal phalanges was available. These were embedded in celloidin and stained with hematoxylin-eosin. Much help in the interpretation of the changes in these structures was given by Dr. Granville Bennett.

"In all of the sectioned phalanges, there were qualitatively similar changes but there were some differences in extent and distribution. In two, the alterations were much severer in the distal half than in the proximal; in the other two, they were more marked in the central portion than at either the proximal or the distal end. Microscopic study of the sections showed a resorptive process of the osteoclastic type. This was distributed in focal areas, rather than generalized, as it is in hyperparathyroidism. In association with the resorptive process there was a proliferative one, resulting in the production of very abundant osteoid matrix. This matrix was formed along otherwise normal trabeculae but did not calcify so readily as the usual osteoid matrix. The osteoid, however, resulted in apparently slow formation of trabecular bone in a bizarre architectural pattern with quite imperfectly formed lamellae. The lacunar spaces of these lamellae were more rounded than usual, and the canaliculi radiating out from them were less uniform and less evenly distributed than in normal bone. Often there were no sharply defined lamellae and the whole bone had a faintly basophilic quality. The cellularity of the osteoid varied greatly from place to place. There were wide areas without a single cell in the osteoid matrix, while in other areas the cellular content approached that of normal osteoid. Near the articular cartilage there was much less change, but even here a little overproduction of osteoid with elongation and distortion of the cartilage column was apparent.

"The areas corresponding to the regions described roentgenologically as ones of 'cyst' formation were composed of tightly packed, fully mature collagenous connective tissue without any admixture of bone or osteoid. In no portion of the material was there a suggestion of neurofibromatosis or any form of neoplasm."

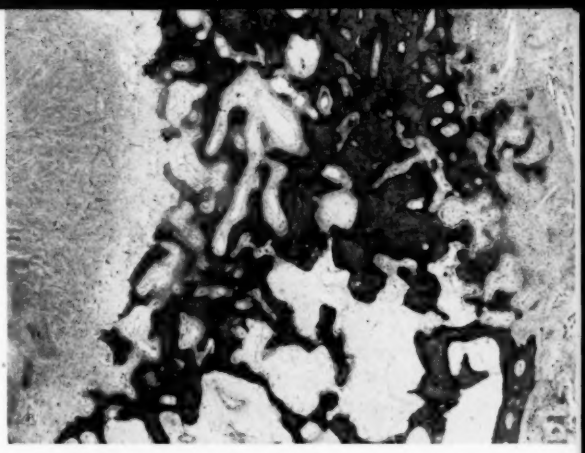


Fig. 3.—Areas from distal phalanx of right ring finger showing resorption of osteoclastic type, together with an adjoining proliferative process characterized by a very abundant osteoid matrix formed around otherwise normal trabeculae. This has resulted in the apparently slow formation of a bizarre architectural pattern.

COMMENT

At least 50% of patients with tuberous sclerosis demonstrate intracranial calcification in the region of the basal ganglia. A small number present calcification in the region of the dentate nuclei of the cerebellum, as does this case. The osseous changes that have been described in clearly delineated cases are limited chiefly to (1) islands of increased density in the calvaria overlying the cortical nodules and shown in a previous report, as in this case, to be osteosclerosis confined to the trabeculae of the diploic spaces; (2) punched-out, cyst-like foci in the phalanges of the hands and feet, and (3) an irregular, wavy periosteal change in the metatarsals and metacarpals. The periosteal changes seem to have a predilection for the feet, while the cyst-like changes of the phalanges are commoner in the hands.

The lesions in the phalanges of this patient are unlike those of other diseases of bone. It does not resemble fibrous dysplasia of bone. The type of osteoid is similar to that seen in Milkman's disease, but the distribution of lesions is entirely different. The resorptive phase is somewhat like that seen in the bone changes secondary to renal failure, but the disease picture as a whole is not

similar. While this description is based on a single case, it is possible that the changes in the phalanges represent a process unique to tuberous sclerosis.

As an interpretation of the histologic sequences involved in this lesion, it is suggested that there was a resorptive phase, followed by a building phase. In the irregular progression of these two phases, there could be periods when, in the building phase, the tissue cells became mature and able to form only fibrous tissue, rather than bone. The confluence of such areas of mature fibrous tissue would then result in the regions which appeared as "cysts" in roentgenograms. Imperfect bony replacement could give rise to zones of increased density at the margins of the areas of mature fibrous tissue, thus heightening the contrast in the roentgenograms. Brooks and Lehman [3] have offered a similar suggestion in explaining the roentgenographic appearance of subperiosteal cysts in neurofibromatosis.

There are a number of disease entities characterized by fibrous replacement of bone. No unanimity of opinion exists regarding the basic pathologic processes and proper classification of the many lesions in the whole group. The histopathologic structure of the cyst-like lesions from the case here presented apparently adds one more condition to an already puzzling situation; therefore, this material is presented from a purely descriptive standpoint. It is not now possible to place it in proper perspective with regard to lesions of somewhat similar nature found in other disease entities. At Dr. Bailey's request, sections from this material have been reviewed both by other neuropathologists and by other pathologists with considerable interest and experience in lesions involving bone. All agreed that, while the material shows some features in common, it is somewhat different from any heretofore described. Any attempt at classification would only add to an already confused picture.

In view of the interrelationship of the various manifestations of the neurocutaneous syndromes, it has been speculated that the osseous lesions occurring in tuberous sclerosis might be similar to those in neurofibromatosis. In closing the discussion of his paper on roentgenographic changes in the cranium in cases of tuberous sclerosis, Yakovlev [4] remarked, "Many analogies between tuberous sclerosis and neurofibromatosis lead one to think that the bone changes in the two conditions may be similar." In neurofibromatosis, the significant lesions are tumors with their origin from cells of the nerve sheaths, either (1) from cells of the mesodermal elements of the sheaths or (2) from cells of neuroectodermal origin of the sheaths of Schwann. The cyst-like lesions of the bone were assumed to be replacement or destruction of bone by pressure or invasion by tumor masses composed of such cells arising from nerves within periosteum or bone. However, a study of reported cases in which such lesions have been examined histologically shows relatively few instances in which this is so. Usually, the bone is replaced by nonspecific fibrous connective tissue.

Berland states that cystic changes in the phalanges similar to those found in tuberous sclerosis may be found in von Recklinghausen's disease, where there are multiple areas of bone absorption with true cyst formation, and that these occur anywhere within the diaphysis. The lesions from our case certainly are not rue cysts. We have pointed out that roentgenographically these lesions in the phalanges most closely resemble those seen in sarcoidosis. There are reports of cystic changes in the vertebrae and in the shafts of the long bones in cases of tuberous sclerosis. The description of the patients in reports of such cases leads to serious doubt that the clinical findings warrant a diagnosis of tuberous sclerosis. We have never encountered these spectacular findings in any of our cases.

Tumors of organs other than the brain have long been known to occur in patients with tuberous sclerosis. Probably the most frequent and the best known are the tumor masses occurring in the kidneys. These usu-

ally are of mixed type, and a wide variety of names has been applied, such as fibrolipomyangioma, adrenorhabdoleiomyoma, etc. Lesions have been found in other organs—heart muscle, lung, thyroid, spleen, and retina, as well as the skin. In all the involved organs, the tumors are usually regarded as tissue malformations rather than true neoplasms; malignant degeneration or true neoplasia is rare, and apparently restricted to the renal tumors. Thus, the concept has been proposed that the whole tuberous sclerosis complex is characterized by disseminated hamartomatosis, arising from faulty differentiation of tissues in the involved organs. By some, the lesions of neurofibromatosis are also considered to be of hamartomatous origin. If this concept is correct, the lesions described in the phalanges of the present case may possibly represent a further manifestation of the hamartial nature of tuberous sclerosis. At present, this does not seem likely.

The distribution of these particular lesions is of interest. Holt and Wright [5] found no evidence of lesions in the phalanges of 127 cases of neurofibromatosis, and I have found no instances in the literature. In polyostotic fibrous dysplasia, the fibrous lesions appear within the interior of the involved bones, distending their contours, and are nearly always limited to the shaft. The transient cortical defects found in growing tubular bones likewise are found in the shafts. Of the lesions of bone found in the phalanges which are not characterized by fibrous displacement—gout, arthritis, enchondroma, sarcoidosis—none produces a picture likely to be confused with the phalangeal lesions of tuberous sclerosis. The distribution of these lesions is pathognomonic; one must wonder why they are so situated.

SUMMARY

It has been possible to study the typical cyst-like lesions found in the phalanges of a patient with tuberous sclerosis. These lesions are shown to be not cysts, but areas of nonspecific fibrous replacement of bone, encompassed by a proliferative process resulting in an abundant osteoid matrix. Thus far, the entire process, both in structural detail and in distribution, appears to be peculiar to tuberous sclerosis. Similar fibrous replacement is found in other disease entities, but the material from this one case is not sufficient to place it in proper classification with regard to these other entities.

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Affective Disturbances in Brain-Damaged Patients

Measurements with the Minnesota Multiphasic Personality Inventory

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While intellectual effects of brain damage have been studied extensively using both experimental methods and standardized measuring instruments, possible affective defects have generally been only commented upon and grossly described. Several papers have appeared recently, however, which have attempted to describe patterns of emotional disturbance characteristically found in brain-damaged patients.* These investigators used the Minnesota Multiphasic Personality Inventory and have described significant differences in patients with frontal and patients with parietal damage. Results from patients with frontal damage have been characterized by a denial of anxiety, attitudes of acceptance, affability, and self-confidence, schizoid trends, and rather low levels of aspiration. Parietal lesions seem to cause a preponderance of neurotic-like symptoms, such as anxiety, depression, guilt, introversion, feelings of inadequacy, and somatic concern. The extent to which these affective symptoms of brain damage are similar to those in patients with psychotic and neurotic disorders may provide a basis for more effective treatment of affective disturbances in brain-damaged patients.

This study was supported in part by a grant from the James Whitcomb Riley Memorial Association.

From the Department of Surgery, Section of Neurological Surgery, Indiana University School of Medicine.

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MATERIAL AND METHODS

Problem.—The problem in this investigation was (*a*) to determine the typical profiles for groups of patients with and without brain damage and (*b*) to describe the differences and similarities in affective symptoms found in intergroup comparisons.

Population.—The patients used were the same as those reported in two previous studies.† The groups will be described very briefly, since the nature and rationale of their composition have been presented previously.[3] Fifty patients with proved brain damage or dysfunction composed one group, and the second group consisted of 50 persons with negative neurological and anamnestic findings of organic brain involvement, although many had definite neurotic symptoms. The subjects in the two groups were very closely matched in pairs on the basis of color, sex, chronological age, and years of formal education, in an attempt to equate sources of variability irrelevant to the problem.

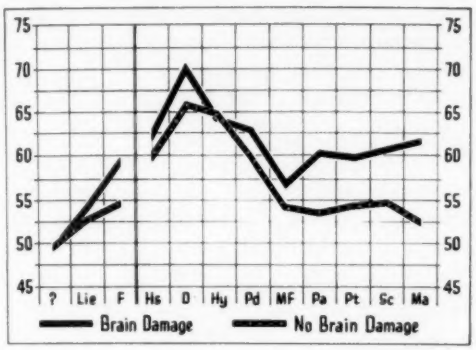
Procedure.—The Minnesota Multiphasic Personality Inventory was administered individually to each patient, and the scoring was completed before either group was composed. Although this test has been used rather extensively in clinical practice and research,[5] it may be appropriate to describe briefly its construction and purpose. The test consists of 550 statements, each printed upon a separate card. The statements refer to various aspects of the subject's feelings, symptoms, and behavior, including health, sexual adjustment, social attitudes, family life, general feeling tone, and interests. The subject is asked to sort the cards into True or False categories as they apply to him at the present time. Nine scales have been devised upon which the subject's responses are rated: Hypochondriasis, Depression, Hysteria, Psychopathic Deviate, Masculinity-Femininity (of interests), Paranoia, Psychasthenia, Schizophrenia, and Mania. These scales were developed on an entirely empirical basis through comparison of the answers given by carefully diagnosed psychiatric groups and a large group of normals. For example, answers differentiating the group of patients with the diagnosis of depression as contrasted with the normals contributed to the depression scale. No a priori notions

† References 3 and 4.

regarding how patients should answer the questions, but, rather, only the obtained results, were used.

The test also includes four so-called validating scales, three of which we have used. These are the ?, Lie, and F scales. The ? scale is a reflection of the number of items placed in a "Cannot Say" rather than the True or False category, and thus represents the number of items which the subject has dropped from consideration. The Lie scale is based upon items which most subjects would almost certainly have to answer truthfully in only one way, and represents the number of answers contradicting this general trend. The F scale comprises items which are answered in a certain way by all but a very small percentage of the general population. A high score on this scale indicates either inconsistency of responses through carelessness, uncooperativeness, or confusion, or deliberate answers by the subject designed to depict himself in an unfavorable light.

Means and standard deviations were calculated for each scale. Intergroup statistical comparisons of the mean differences were made by use of the *t* technique, employing the method for correlated groups.



Graphic presentation of mean scores obtained by equated groups with and without brain damage on the Minnesota Multiphasic Personality inventory.

Means, Standard Deviations, t *Ratios, and Probability Levels Comparing Groups of Fifty Paired Patients With and Without Brain Damage*

Groups	?	Lie	F	Hs	D	Hy	Pd	MF	Pa	Pt	Sc	Ma
Brain damage												
Mean	50.00	54.37	59.76	62.66	70.93	64.05	63.41	57.02	60.59	59.93	61.10	61.98
S. D.	0	5.29	9.86	12.35	16.92	13.04	10.42	9.79	12.05	12.33	13.98	12.53
No brain damage												
Mean	50.00	53.11	55.00	60.55	66.45	64.82	59.74	54.08	58.74	54.63	55.00	52.74
S. D.	0	4.56	6.07	10.40	15.54	11.37	11.55	9.63	9.64	12.07	9.79	10.43
t ratios	0	0.69	2.14	0.76	1.07	−0.33	1.29	1.57	2.66	2.51	2.84	4.55
P <	ns	ns	0.05	ns	ns	ns	ns	ns	0.02	0.02	0.05	0.001

RESULTS

The Table presents means, standard deviations, *t* ratios, and probability levels.

It may be noted by inspection of the means that the profiles for the two groups are generally similar, but that the brain-damaged group tends to deviate in the direction of higher values on the last four scales. A comparison of the mean results is facilitated by a graphic representation, which is shown in the Chart.

The various scales are indicated along the horizontal axis, and the obtained means, along the vertical axis. The scores along the vertical axis are T scores, which have the advantage of permitting direct comparison of the present results with those obtained in the original standardization of the test. A T score of 50 on any scale represents the mean for the original standardization group, and may be thought of as approximately the average score for a normal population. Ten points on either side of a T score of 50 represents one standard deviation. The degree of deviation of the results for our groups from the expected (normal) results may, therefore, be easily estimated.

The over-all shape of the curves is markedly similar for the two groups. The outstanding differences in the curves are present on the last four scales, Paranoia, Psychasthenia, Schizophrenia, and Mania. The probability of the mean differences occurring on a chance basis are indicated in the Table. The difference with relation to variability of the differences on the Mania scale, for example, could have happened less than 1 in a 1000 times on a chance basis.

Previous investigation of the meaning of the MMPI results has indicated that the

scales for Hypochondriasis, Depression, and Hysteria are typically elevated for neurotic patients and have been called the "neurotic triad." [6] The curve for our group without brain damage fits this pattern nearly perfectly, and undoubtedly is a reflection of our deliberate inclusion of many neurotic patients. The curve for the brain-damaged group, however, also shows its maximal height for these scales, and the statistical comparisons indicate insignificant mean intergroup differences on these variables. The last four scales in the Chart have been interpreted as measuring more serious and peculiar deviations of thought processes, and it is on these variables that the brain-damaged subjects show their major deviation from the controls.

COMMENT

We should recognize before interpreting the results of this study that the brain-damaged group was composed of patients with lesions heterogeneous with respect to type, extent, and location. The results may be taken to describe the findings in brain damage generally rather than in groups specific for diagnosis or location of lesions. Previous attempts have been made to differentiate the effects on the MMPI of frontal and parietal damage.‡ The curve for our brain-damaged group describes the elevation of scores on the "neurotic triad," which is supposedly typical of posterior brain damage, as well as an increase on the variables associated with more serious psychopathology, such as was found in groups with frontal damage. This result may very possibly reflect the heterogeneous nature of our brain-damaged group.

The results of this study suggest that affective disturbances primarily of a neurotic-like nature are the rule rather than the exception in brain-damaged patients. Although symptoms such as anxiety, concern over bodily functions, and depression may have quite a realistic basis, depending upon the nature of somatic symptoms produced by brain damage, recognition of their presence should encourage therapeutic attempts to alleviate the distress they represent.

‡ References 1 and 2. Friedman, S. H.: Psychometric Effects of Frontal and Parietal Lobe Brain Damage, Ph.D. thesis, University of Minnesota, 1950.

SUMMARY AND CONCLUSIONS

The Minnesota Multiphasic Personality Inventory was administered to groups of 50 patients with and without brain damage who were individually paired on the basis of color, sex, chronological age, and years of formal education. The group without brain damage included a large proportion of neurotic patients. Intergroup comparisons of the results indicated that brain-damaged patients typically experience neurotic-like symptoms of anxiety, hysteria, depression, and concern over bodily functions. Mean differences on the scales for these variables between the group with and the group without brain damage were statistically insignificant.

Significant differences between the groups occurred on the scales which are ordinarily associated with severer mental disturbances —Paranoia, Psychasthenia, Schizophrenia, and Mania. The brain-damaged group had the higher values on these scales. Recognition of the neurotic-like symptoms which seem typical of brain damage emphasizes the need for treatment aimed toward the alleviation of such symptoms.

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Comparative Study of Thiamylal and Thiopental (Pentothal) in Electroconvulsive Therapy

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Thiamylal (Surital) sodium has been reported* to be a thiobarbiturate of exceptional value as premedication in electroconvulsive therapy, particularly by abolishing or minimizing the convulsion. Thus, electroconvulsive therapy could be given safely to those with bony or other conditions wherein it would be unwise for the patient to have a generalized, intense convulsive seizure.

The purpose of the present clinical study was to compare thiamylal with thiopental (Pentothal) as a premedication for patients receiving electroconvulsive therapy to determine any significant differences.

METHOD

A group of 25 patients who required electroconvulsive therapy were selected at random. There were 15 women and 10 men, with an age distribution from 21 to 80 and an average age of 45. The method of "blind study" was used; i. e., four differently labeled vials individually containing thiobarbiturates A, B, X, and Y were supplied by Abbott Laboratories. The only discernible difference in the vials was the label. Otherwise, the vials themselves and the contained powdered thiobarbiturates were identical in appearance.

After the study was completed, we were informed that vials labeled A and X were both thiamylal, whereas vials labeled B and Y were thiopental.

From the Los Angeles Neurological Institute.

* References 1, 2, and 3.

Each patient included in this study had a minimum of eight treatments, so that every patient could be premedicated twice with A, B, X, and Y. The observations made represent the pooled efforts of a skilled and experienced treatment team of two nurses and myself.

Each patient received an intravenous injection of a 2.5% solution of thiobarbiturate A, B, X, or Y during a two-minute period, in sufficient quantity to produce a state of anesthesia deep enough to prevent the patient from responding to sound, sight, and touch. The amount of the drug used varied with each patient from 2½ to 6 grains (0.15 to 0.40 gm.), depending upon the various factors which modify individual susceptibility and tolerance.

In addition to and along with the unknown thiobarbiturate, each patient was given 1/50-1/75 grain (1.20 to 0.8 mg.) of atropine intravenously, depending upon the patient's weight. It is possible that the use of atropine might have obscured the pure effects of the individual thiobarbiturates had they been used alone. However, I feel that with all electroconvulsive therapy, no matter what other drugs are used as premedication, if there is no specific contraindication, atropine should be used regularly. It provides a large safety factor by stimulating respiration, and preventing vasovagal cardiac irregularities, nausea, excessive salivation, and mucus production.

The treatment current was applied immediately after the patient was adequately anesthetized. In our treatments, we use the Electronicraft instrument, which permits the use of a glissando technique[4] in inducing the convulsion; that is, it permits a gradual rise of the current with a resulting smoother induction of muscular contraction, rather than the jarring movement that follows sudden application of full current with closure of the switch. The current is first brought to a peak level of 400 ma. and then dropped to 100 to 150 ma. Although it is possible to produce a convulsive seizure at below 400 ma., we have found that if the current is brought to this maximal level, there is a shorter period of apnea. Furthermore, main-

tenance of the current at between 100 and 150 ma. during the remainder of the convulsive seizure cuts down the excursion of gross movements in the clonic phase of the seizure.

It may be that the use of the Electronicraft instrument obscured the degree of apnea produced by each thiobarbiturate. It is likely that the technique of treatment as above described produces specific central respiratory stimulation which counteracts some of the depressing effect of the thiobarbiturates. Since I have used this technique with Electronicraft equipment, apnea has rarely been prolonged, and never dangerous.

CLINICAL OBSERVATIONS

The pooled clinical observations revealed that no significant differences between thiamylal and thiopental could be established when atropine was used concurrently with each, and the above-described technique of electroconvulsive therapy was used. The following observations were made:

1. *Rapidity of Action.*—Both thiamylal and thiopental are very quick-acting, with no discernible differences.

2. *Intensity of Convulsion.*—In no case did we observe abolition of convulsions. However, there seemed to be perceptible "softening" as compared with what is ordinarily observed in unpremedicated patients. This group of 25 patients, however, received no treatment without premedication, so that the impression of "softening" of the convulsion is a purely clinical and uncontrolled observation. Of 200 recorded treatments, 9 were recorded as coming close to complete abolition of the seizure. However, this occurred as frequently with thiopental as it did with thiamylal.

3. *Duration of Convulsion.*—The time varied in all 200 recorded treatments between 10 and 45 seconds, the average being about 28 seconds, with no appreciable difference between the two thiobarbiturates. However, it seems apparent that the use of either thiobarbiturate shortens the seizure as compared with the duration of seizure in an unpremedicated patient.

4. *Duration of Apnea.*—Significant differences were absent using the above-described technique of treatment. In all 200 treatments there were no notable instances of prolonged apnea with the amounts of thiobarbiturates used. The danger of prolonged apnea is in direct proportion to the dosage of thiobarbiturate.

5. *Time to Consciousness.*—This was highly variable, from 10 minutes to 50 minutes and varied with the dosage used, but no significant differences were observed between the two thiobarbiturates. The post-shock after-effects of the two were essentially similar, and no significant differential findings could be made. With both, post-treatment excitement or bewilderment, or intense drowsiness was absent.

6. *Blood Pressure and Pulse.*—Thiamylal and thiopental had a "normalizing" effect. Rises in blood pressure and pulse rate were relatively small when taken within several minutes after the convulsion, but no significant differences were found in the action of the two thiobarbiturates. All patients under treatment were normotensive for persons of their age.

7. *Special Complications.*—A. Laryngospasm: This occurred in mild form three times out of the total of 200 treatments, twice with thiamylal and once with thiopental.

B. Muscle Strain: Four patients complained of mild back pain. Examination revealed nothing more serious than the common muscle strain which is so often seen in electroconvulsive therapy, and which disappeared as treatment progressed. There were no other musculoskeletal injuries. The use of one or another thiobarbiturate could not accurately be related to the occurrence of muscle strain. It appears that any of the thiobarbiturates serve to allay apprehension prior to the application of the electric stimulus, thereby reducing neuromuscular tension and thus softening the convulsion. Other alterations of cerebral physiology resulting from the use of either thiobarbiturate may cause modifications in the pattern of the convulsion.

It is our practice to use succinylcholine chloride intravenously when it is indicated that the convulsive seizure be abolished or minimized. With adequate dosage of this

medication, this objective is not a chance result, since the drug acts specifically to paralyze the neuromuscular junction. With adequate precautions and equipment for assistive respiration, we find succinylcholine (Anectine) very useful and safe, along with a thiobarbiturate. The thiobarbiturate allays the anxiety. The succinylcholine softens or abolishes the muscular movements and protects against laryngospasm.

SUMMARY

Twenty-five randomly selected patients who required electroconvulsive therapy were observed during the course of 200 electroconvulsive treatments. Each patient received a minimum of eight treatments, premedicated with thiamylal (Surital) and atropine, or thiopental (Pentothal) and atropine.

The method of "blind study" is described and was used in this project to test clinically and compare thiamylal with thiopental as premedication for electroconvulsive therapy.

No significant differences between these two thiobarbiturates could be demonstrated. They serve equally well as premedication in electroconvulsive therapy and should be used in conjunction with atropine.

If minimization or abolition of the convulsive seizure is deemed clinically advisable for any reason, the use of succinylcholine (Anectine) for this purpose, rather than any of the thiobarbiturates, is recommended.

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Determination of Serum Proteins and Polysaccharides

Comparison of Neoplastic Diseases, Particularly of the Central Nervous System

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Tönnies,[1] in a review of the literature on the changes in the serum proteins due to tumor growth, notes that a high globulin-to-albumin ratio has been found consistently in association with human cancer. This observation, based upon studies employing the older techniques of protein chemistry, has been confirmed by the newer method of electrophoresis of moving boundaries.[2] Janssen,[3] also using electrophoretic methods, found an increase in the gamma globulin content of the serum from patients with cancer in the pancreas or liver. Rundles and associates[4] found hypoalbuminemia and increases occurring in the various globulin fractions in patients who were seriously ill with chronic lymphocytic leukemia, with chronic granulocytic leukemia, or with acute or subacute leukemia.

More recently, paper electrophoresis has been used for the analysis of serum proteins.* Knedel and Zettel[8] applied the method to cases of bronchial carcinoma and found a significant increase in the alpha-2 globulin in the majority of the cases. Luhrs and associates[9] used both the electrophoretic and the salt precipitation method and reported a difference in the protein patterns in carcinoma cases with and those without metastases, the former group being characterized by increases of the alpha-2 and beta globulins.

Carbohydrates are associated with serum proteins, and increases in the polysaccharide content of serum have been reported in carcinoma.† Fractionation of the serum proteins by salt precipitation indicated a greatly increased polysaccharide content of the albumin fraction.‡ Weimer and co-workers[13] used a low-temperature ethanol fractionation method and found only a small amount of polysaccharide combined with albumin.

Recently the technique of paper electrophoresis has been used for the separation and estimation of the carbohydrates associated with serum proteins. The method, however, involves certain technical difficulties, since the paper is also carbohydrate in nature, and consequently only a limited amount of data from its application have appeared § and no normal values have been established. The present paper describes the application of paper electrophoresis to a study of the protein and carbohydrate distribution in various forms of primary and metastatic brain tumors. For the purpose of comparison, other forms of malignant disease were studied, including leukemia.

Diana M. Temple and Joseph Murphy gave technical assistance. Drs. D. O'Doherty, K. Lewis, E. C. Rice, and W. T. Spence supplied the blood samples, and the Neurology and Neurosurgery Services of the U. S. Naval Center, Bethesda, Md., cooperated in this study.

From the Departments of Biological Chemistry and Neurology, Georgetown University School of Medicine.

* References 5, 6, and 7.

† References 10 and 11.

‡ References 11 and 12.

§ References 14 and 15.

MATERIAL AND METHODS

Clotted blood, from fasting patients, was centrifuged after standing for three hours. In most cases the blood samples were taken shortly before surgery and analyzed within 24 hours. Only those cases were included in which the diagnosis had been made after histological examination of the tissue sections.

For the protein analyses the method of paper electrophoresis previously reported was used.[16] The only innovation was the substitution of zinc sulfate for mercury bichloride in the solution used to stain the proteins on the paper strip ‖; this change in no way affected the quality of the pattern.

For the determination of the total polysaccharides the Badin [17] modification of the tryptophan method of Shetlar and associates [18] was used. It was found advantageous to dilute 1 part of the serum with 2 parts of 0.9% NaCl solution; 0.2 and 0.1 ml. aliquots were used for the analysis of the normal and the pathological sera, respectively. After precipitation of the polysaccharides with 10 ml. of cold ethanol and centrifugation, the precipitate was washed twice with cold ethanol to remove completely the free sugars.

The polysaccharides are combined with the serum proteins and, therefore, move in an electric field. The electrophoretic method used for the determination of the serum protein distribution was also used for the polysaccharides.[16] In order to assign the proper position of the polysaccharides in relation to the carrier proteins, it is necessary that the sample strips be placed side by side in the electrophoresis apparatus. For the proteins 0.01 ml., and for the polysaccharides 0.04 ml., was used. The protein strip was stained as described and was used as the reference strip in subsequent measurements of the polysaccharides.

The polysaccharide strip was stained by a modification of the method of Köiw and Grönwall.[14] The method depends upon periodate oxidation and subsequent color formation with the Schiff reagent and must be carried out precisely as described. Since certain technical difficulties are involved and the modification is as yet unpublished, Grönwall and Bjornesjo have allowed us to describe the complete procedure so that other investigators may avoid the pitfalls.

Reagents for Polysaccharide Staining.

Periodic Acid: Periodic acid, 2.4 gm., is dissolved in 450 ml. of distilled water, to which is added 0.5 N sodium acetate solution to bring the pH to between 3.0 and 3.3. The pH should be determined with a pH meter; the resulting solution is usable for one to two weeks if it is stored in the dark.

Reducing Solution: Potassium iodide, 15 gm., and sodium thiosulfate, 15 gm., are dissolved in 1 liter of distilled water. Immediately before use, 2 N hydrochloric acid solution is added in the ratio of 1 part of acid to 100 parts of solution.

Fuchsin Sulfite Solution: Fuchsin sulfite, 2 gm., is dissolved in 400 ml. of boiling water; after the solution has cooled to 50 C, it is filtered. To the filtrate 10 ml. of 2 N hydrochloric acid solution and 4 gm. of potassium pyrosulfite (metabisulfite) are added. The solution should be kept in a well-stoppered bottle in the cold room. On the following day 1 gm. of decolorizing carbon is added, mixed, and filtered immediately. About 10 ml. of 2 N hydrochloric acid solution is added to the filtrate, in small aliquots, until the mixture does not turn a violet-red color when allowed to dry spontaneously on filter paper at room temperature. The solution should then be stored in the cold room.

Sulfite Rinse Water: Potassium metabisulfite, 4 gm., is dissolved in 1 liter of distilled water; 10 ml. of concentrated hydrochloride acid is added.

Drying, Fixing, and Staining of Strips.

1. Dry at 100 C for 10 minutes.
2. Fix in ethanol for 5-10 minutes.
3. Place in periodic-acid solution for seven minutes.
4. Rinse in distilled water.
5. Place in reducing solution for two minutes.
6. Rinse carefully in distilled water.
7. Place in fuchsin sulfite solution until maximum color develops, 15 minutes.
8. Rinse in sulfite rinse water.
9. Leave in sulfite rinse water for 1 hour, changing the rinse water at the end of 30 minutes.
10. Dehydrate with ethanol; dry in open air on glass plate.

The strips are read in the densitometer, using Filter 495.

RESULTS

The distribution of the serum proteins and the total polysaccharide content of the malignant neoplasms affecting the central nervous system are given in Table 1, together with the standard deviations. Similar data on the carcinoma and leukemia cases are presented in Table 2. Data on six cases of nonmalignant tumors and one tuberculoma of the central nervous system are given in Table 3. For purposes of comparison, the average values for all types of malignant disease, the benign tumors, and the normal are summarized in Table 4.

The *t* values, as measures of significant deviation from the normal, were calculated

‖ Durrum, E.: Personal communication to the authors.

TABLE 1.—*Serum Proteins and Total Polysaccharides in Malignant Tumors of the Central Nervous System*

Case No.	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %	Polysaccharide, Mg/100 Ml.	Diagnosis
250	41.4	4.4	13.7	21.4	19.4	177	Medulloblastoma
267	41.2	6.9	13.5	16.4	21.9	188	Astrocytoma
281	34.6	7.9	20.1	15.8	21.6	240	Cerebellopontine tumor
360	23.8	9.2	19.3	13.1	34.6	202	Carcinoma of spinal cord, metastatic
364	33.5	3.8	16.3	16.5	29.9	102	Carcinoma of spinal cord, metastatic
381	33.7	11.3	18.4	18.7	17.9	203	Medulloblastoma
423	38.4	4.0	15.2	25.2	17.2	160	Metastatic carcinoma—brain
426	43.0	2.2	8.2	18.1	29.1	183	Glioblastoma multiforme
436	47.0	6.8	15.4	7.7, 6.8 *	16.3	193	Glioblastoma multiforme
453	37.9	8.5	24.8	13.5	15.9	235	Metastatic carcinoma—brain
Average	37.5±6.3	6.5±2.8	16.5±4.4	15.7±4.1	22.4±6.5	194±27	

* Case 436 gave two beta globulin peaks.

TABLE 2.—*Serum Proteins and Total Polysaccharides in Carcinoma and Leukemia*

Case No.	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %	Polysaccharide, Mg/100 Ml.	Diagnosis
Carcinoma							
256	43.5	4.2	10.4	12.5	29.4	228	Cervix; died
257	45.5	10.9	14.1	9.0	20.5	225	Cervix
273	33.1	9.0	20.4	13.8	23.7	153	Bronchogenic; died
274	34.7	8.1	13.3	16.9	27.0	224	Bronchogenic; died
275	32.7	5.7	17.9	20.0	23.7	408	Mouth, metastatic
276	45.2	4.7	10.6	14.0	25.5	168	Mouth
277	35.5	7.8	19.0	12.1	25.6	191	Mouth
Average	38.6±5.7	7.2±2.4	15.1±4.0	14.0±3.5	25.1±2.8	228±77	
Leukemia							
367	53.4	3.4	11.2	11.2	20.8	89	Myelogenous, chronic
370	36.5	9.1	22.4	17.6	14.4	170	Lymphatic, acute
374	43.5	3.2	4.6	18.4	30.3	124	Lymphatic, acute
387	37.0	11.6	10.0	21.6	19.8	81	Granulocytic, chronic
389	36.3	8.7	8.7	14.0	32.3	128	Lymphatic, acute
398	34.7	10.6	14.7	13.5	26.5	87	Lymphatic, acute
406	37.6	7.4	20.0	17.1	17.9	141	Lymphatic, acute
454	43.4	7.1	12.1	12.1	25.3	142	Lymphatic, acute
455	54.4	2.6	10.1	12.9	19.0	117	Lymphatic, acute
456	55.3	...	16.7	16.1	11.9	124	Lymphatic, acute
457	51.4	3.8	11.9	3.9, 13.1 *	15.1	128	Lymphatic, remission
Average	43.9±8.3	6.8±3.1	13.0±5.1	15.6±3.3	21.2±6.3	121±27	

* Case 457 gave two beta globulin peaks.

TABLE 3.—*Serum Proteins and Polysaccharides in Benign Tumors of the Central Nervous System*

Case No.	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %	Polysaccharide, Mg/100 Ml.	Diagnosis
222	42.7	2.3	4.7	13.9	36.4	163	Tuberculoma
245	39.1	7.0	15.4	14.4	24.1	168	Ependymoma
354	50.0	5.6	11.7	7.5	25.1	102	Meningioma—optic nerve
359	31.4	6.8	19.8	15.9	26.1	155	Ependymoma—spinal cord
379	33.5	3.3	13.7	21.5	28.0	107	Acoustic neuroma
380	33.4	5.2	17.2	24.4	19.8	166	Ependymoma—fourth ventricle
Average	38.3±6.4	5.0±2.1	13.7±5.8	16.3±6.7	26.6±5.8	144±34	

TABLE 4.—*Summary of Average Values of Serum Proteins and Total Polysaccharides*

	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %	Polysaccharide, Mg/100 Ml.
Nervous system, malignant	37.9±6.3*	8.5±2.8	16.5±4.4*	15.7±4.1*	22.4±6.5	194±27*
Benign	38.3±6.4*	5.0±2.1	13.7±5.8*	16.3±6.7*	26.6±5.8	144±34
Carcinoma	38.6±5.7*	7.2±2.4*	15.1±4.0*	14.0±3.5	25.1±2.8	228±77*
Leukemia	43.9±8.3*	6.8±3.1*	13.0±5.1*	15.6±3.3*	21.2±6.3	121±27
Normal	62.3±3.6	3.7±1.5	7.9±1.9	9.6±1.4	16.7±3.3	110±15

* Significantly different from the normal.

TABLE 5.—*Normal Serum Polysaccharide Distribution*

	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %
	9.0	13.1	22.2	35.9	19.8
	12.5	25.8	19.7	22.0	20.0
	15.0	23.2	20.0	29.3	12.0
	9.7	20.2	19.5	33.4	17.2
	9.5	24.4	25.7	20.4	20.0
	11.7	23.7	25.8	26.8	12.0
Average:	11.2±1.8	21.7±4.5	22.2±2.9	27.0±6.1	16.9±3.9

TABLE 6.—*Serum Polysaccharide Distribution in Malignant Disease of the Central Nervous System*

Case No.	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %
250	5.5	25.0	44.5	16.8	8.2
360	8.1	31.5	34.6	14.9	10.9
364	5.9	28.1	21.8	24.2	20.0
381	4.8	27.2	39.5	13.1	15.4
423	12.0	24.3	27.7	16.8	19.2
426	15.8	33.6	22.8	7.3	20.5
436	7.0	16.4	35.9	21.6	19.1
453	11.0	27.9	35.6	19.4	6.1
Average:	8.7±3.7	26.7	32.8±8.0	16.8±5.2	14.9±5.7

TABLE 7.—*Serum Polysaccharide Distribution in Leukemia*

Case No.	Albumin, %	Alpha-1 Globulin, %	Alpha-2 Globulin, %	Beta Globulin, %	Gamma Globulin, %
370	11.3	26.7	31.5	20.0	10.5
374	6.9	27.1	37.5	8.1	20.4
389	10.0	21.7	25.9	24.1	18.3
456	9.4	28.6	20.6	19.9	21.5
Average:	9.4±1.8	26.0±3.0	28.9±7.1	18.0±6.6	17.7±5.0

for all the average values. In each instance the decrease in albumin was significant at the 0.1% level. The increases in the alpha-2 and beta globulins in the malignant neoplasms of the central nervous system were also significant at the 0.1% level. The increases in the alpha-1, alpha-2, and gamma globulin values for the carcinoma cases were significant at the 1.0% level. In the leukemia cases the increase in the beta globulin level was significant at the 1.0% level. The alpha-2 globulin was significantly increased in all three types of malignant disease; the alpha-1 globulin, in the carcinomas and the leukemias; the beta globulins, in leukemia and the malignant tumors of the central nervous system, while the increase in gamma globulin was significant only in the carcinomas. Significant changes were also found in the alpha-2 and beta globulins in the benign tumors of the central nervous system.

The increases in the total polysaccharide content were significant at the 0.1% level in the malignant tumors of the central nervous system and in the carcinomas; there were no significant increases in the leukemias or the benign tumors.

The normal distribution of the polysaccharides in given in Table 5; the values are expressed as the per cent of the total polysaccharide associated with each of the various protein fractions. Table 6 contains the distribution of the polysaccharides in the malignant neoplasms of the central nervous system and the distributions in four of the leukemia cases are given in Table 7.

The *t* values were calculated to determine if significant variations from the normal existed in any of the several fractions. The increase in the polysaccharide associated with the alpha-2 globulin, and the decrease associated with the beta globulin, in the malignant neoplasms of the central nervous system were both significant at the 1.0% level. In the leukemias the increase in the polysaccharide associated with the alpha-2 globulin was significant at the 1.0% level.

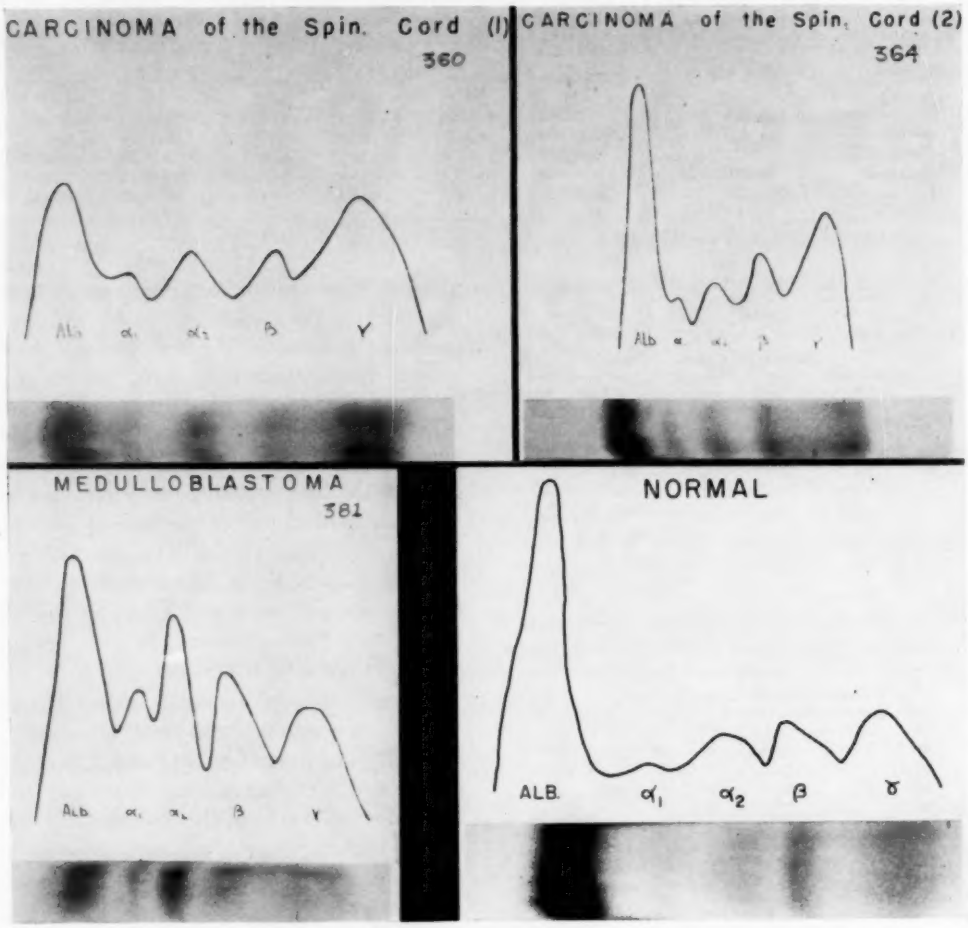

Fig. 1.—Serum protein distribution patterns: Cases 360 and 364, carcinoma of the spinal cord; Case 381, medulloblastoma; a normal pattern.

COMMENT

The changes in the serum protein distribution in the various pathological conditions are best seen by examination of the actual electrophoretic patterns and by the diagrams constructed from the density readings. Several representative patterns are reproduced for illustrative purpose. In Figure 1 are included a normal pattern and the patterns for two cases of metastatic carcinoma of the spinal cord—Case 360, an adenocarcinoma with a high alpha-2 and gamma globulin, and Case 364, a malignant teratoma with increased beta and gamma globulins—and a medulloblastoma (Case 381), with high alpha-2 and beta globulins. In Figure 2, Case 222, a tuberculoma, presents a most unusual pattern, with a gamma globulin peak as high as that of the albumin. In some advanced cases of pulmonary tuberculosis gamma globulin levels as high as those of albumin have been reported.[19] Since no other active tuberculotic lesion could be detected elsewhere in this case, the tremendous increase of gamma globulin must be associated with active antibody formation caused by the tuberculoma. None of the other brain tumor cases showed a similar diagram; the electrophoretic pattern in tuberculoma may have a real diagnostic value. Acute lymphocytic leukemia (Case 406) showed a pronounced alpha-2 globulin peak, and granulo-

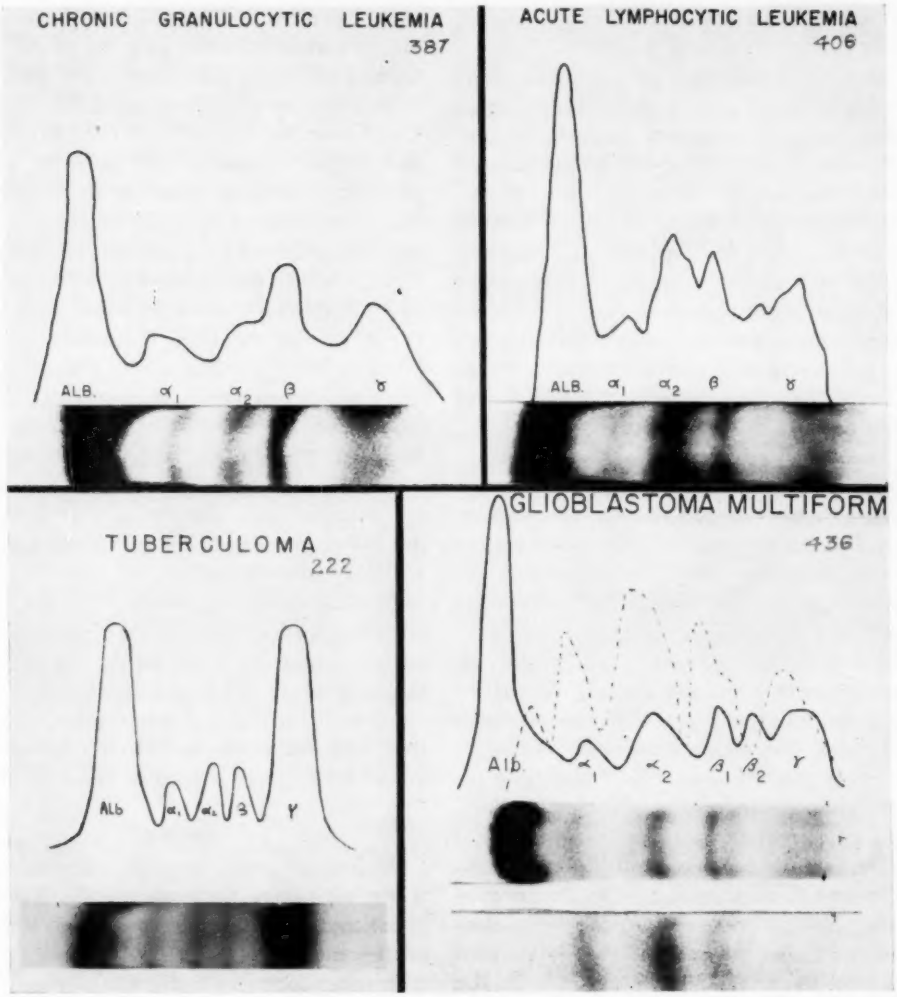

Fig. 2.—Serum protein distribution patterns: Case 387, chronic granulocytic leukemia; Case 406, acute lymphocytic leukemia; Case 222, tuberculoma; Case 436, glioblastoma. The lower pattern and the dotted line represent polysaccharide distribution.

cytic leukemia (Case 387) showed a prominent beta globulin peak.

The serum protein distribution in the carcinoma cases is in good agreement with the findings of Zettel and Endress [20] in 90 cases. The site of the tumor apparently has no effect upon the distribution, according to Esser [21] and Mider [22] and their associates, with confirmation by our data. Luhrs [9] and Wuhrmann and Wunderly [23] state that in metastases beta globulin increases. This observation is not confirmed in our data, since the beta globulins were increased in all cases. That these alterations in protein distribution patterns are not limited to malignant growths affecting the central nervous system is evidenced by the fact that similar changes are found in the benign tumors. Margraf [24] found only minor changes from the normal in the pattern from benign tumors of the stomach, and Shetlar and associates [11] also found normal values in benign tumors. We have found a normal pattern in a woman, now 55, who has a history of a series of benign tumors since early youth. It is apparent, then, that the so-called benign tumors of the central

nervous system are in a different category from that of other benign tumors.

In the leukemia cases the alterations in the protein patterns are not as marked as in the other types of malignant disease. In Case 456, that of a 2.5-year-old Mongoloid girl with lymphocytic leukemia, no alpha-1 globulin could be found in several samples of serum. Case 457 had two definite peaks in the beta globulin region, an observation similar to that of Rundles and associates.[4] These investigators, using the Tiselius method, found an abnormal protein in 6 of 35 leukemic sera, the position of which varied from the beta to the gamma globulin region.

The total polysaccharide content of the serum is significantly increased in malignant disease despite the fact that the protein content remains normal. In most cases of leukemia, however, the polysaccharides are within the normal range. In addition to malignant growths, increases in burns have been reported by Keyser [25] and in tuberculosis by Seibert and associates.¶ The latter investigators suggested that the increase was associated with tissue destruction. Changes in serum polysaccharides have also been reported in pregnancy.#

More important, perhaps, than the total amount of the polysaccharides is their distribution and association with the serum proteins. Using the technique of paper electrophoresis, we found that in normal sera the polysaccharides are associated with the alpha-1, alpha-2, and beta globulins in about the same proportions, and with the albumin to a less extent. These results differ from the findings of some of the earlier investigators * and may be explained by the fact that the salt fractionation method they employed precipitated less of the globulins and increased the polysaccharide content of the contaminated albumin fraction. Weimer and associates,[12] using the low-temperature ethanol fractionation method, found 11% of the total polysaccharides associated with the albumin, a value identical with our own.

¶ References 10 and 26.

References 12 and 27.

* References 4, 12, and 28.

In Figure 2 is shown the polysaccharide and protein distribution in a case of glioblastoma multiforme. It is apparent that the largest fraction of the polysaccharides is associated with the alpha-2 globulin. Wunderly and Piller [15] reported 12 cases in which polysaccharide data were included; among these were 3 cases of malignant disease. In metastasized breast cancer, the highest percentage of polysaccharide was in the gamma globulin fraction; in metastasized liver cancer it was in the alpha-2 fraction, and in Hodgkin's disease, in the beta globulin fraction; no normal values were included. The studies on polysaccharide distribution are in an early stage, and considerable further work is required to establish the significance of these findings, but the present data do point to an increase of the fraction associated with the alpha-2 globulin.

It is likewise suggestive that the total polysaccharide content in the sera from the benign tumor cases is within the normal range, whereas the level is consistently elevated in the malignant tumor cases. If further work shows the same trend, this observation could have diagnostic value.

SUMMARY

With use of paper electrophoresis quantitative studies were made on the blood serum of patients with malignant and benign tumors of the central nervous system in comparison with other forms of malignant disease. All types of malignant disease studied showed a significant increase in the alpha-2 globulin. The alpha-1 globulin was significantly increased in carcinoma and in leukemia. In the malignant tumors of the central nervous system and in leukemia, the beta globulin fraction was also increased. With all of these changes there was a concomitant decrease in albumin.

The increases in total serum polysaccharides were highly significant in malignant tumors, but not in benign tumors or in leukemia. Normal values for the distribution of the polysaccharides in serum were established in terms of the associated proteins. Albumin is combined with the smallest

amount of the polysaccharides among the serum protein fractions. Almost three-quarters of the polysaccharides are distributed equally among the alpha-1, alpha-2, and beta globulin fractions. The polysaccharide distribution in the malignant tumors of the central nervous system was characterized by an increase in the fraction associated with the alpha-2 globulin and a decrease in the fraction associated with the beta globulin. In leukemia there was a significant increase in the fraction associated with the alpha-2 globulin.

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Cerebral Oxygen Uptake in Chronic Schizophrenic Reaction

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Since Kety and associates [1] reported that the cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR_{O_2}) are normal in schizophrenia, patients with this disorder have commonly been used as "normal subjects" for cerebral metabolic studies. In the course of such studies we have noted unusually low values for CMR_{O_2} in approximately one-third of patients with chronic schizophrenic reactions.

Using the original nitrous oxide technique of Kety and Schmidt,* we have made 29 determinations of CBF and CMR_{O_2} upon 24 patients with chronic schizophrenic reactions of two or more years' duration and have compared these with the rates in 81 control cases.

The experimental group consisted of 11 men and 13 women from 16 to 66 years of age, with an average age of 36 years. In these subjects the onset of clearly recognizable schizophrenic reactions had occurred from 2½ to 23 years prior to study; the average duration of illness was 9 years. Distribution of sex, age, and duration of the illness in the group was fairly uniform through the ranges described (Fig. 1). All had been continuously hospitalized for at least one year in a psychiatric hospital at the time of study; many had been hospitalized for much longer periods. Patients with equivocal psychiatric diagnoses, history of brain trauma, infection, or other neurological disease, and patients with other significant medical illness were excluded from the study. Eighteen of the subjects had received somatic treatment for their disorder at varying periods prior to this study; 5 patients had received 50 insulin coma treatments and from 5 to 75 electroshock treatments; 1 patient had received 47 insulin coma treatments; 12 patients had received from 9 to 215 electroshock treatments; 6 patients had received no somatic treatment. All of the subjects were ambulatory within the hospital, physically active, eating normal diets, and participating in treatment programs.

The control group, which consisted of 43 normal subjects, 27 patients with multiple sclerosis, and 11 patients with miscellaneous disorders without cerebral involvement, had a mean CMR_{O_2} of 3.2 ± 0.1 ml. per 100 gm. of brain per minute. The mean CMR_{O_2} of the experimental group was 2.7 ± 0.2. The p value, when rates for control and schizo-

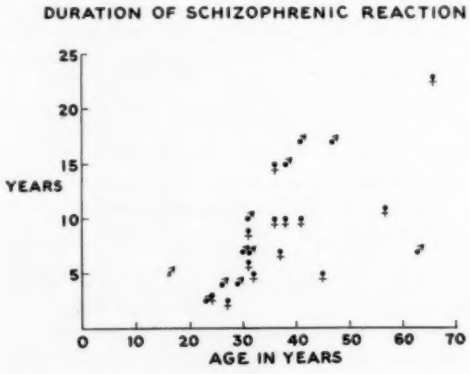

Figure 1

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* References 2 and 3.

phrenic groups are compared, was less than 0.01. The lower rates of chronic schizophrenic patients skew the distribution frequency of CMR_{O_2} to the left when compared with those for the control group or any of its components (Fig. 2). Mean rates of CBF for the control and the chronic schizophrenic group are identical (50 and 48 ml. per 100 gm. of brain per minute respectively).

The 29 determinations upon chronic schizophrenic subjects have been divided into two groups, viz., 11 CMR_{O_2} values of 2.2 or less and 18 values of 2.3 or more. The 11 determinations, which are associated with a CMR_{O_2} of less than 2.3 ml., occurred with a mean CBF of 39 ml. per 100 gm. of brain per minute, while the 18 determinations with the CMR_{O_2} of 2.3 ml. or more occurred with a mean CBF of 54 ml.

Attempts to correlate the clinical features with low rates showed that low rates occurred only in those 10 patients whose disease had existed for four or more years (Fig. 3). Age at onset, sex, severity of disease, frequency of insulin or electroshock therapy, pulse rate, and mean arterial blood pressure were identical in the schizophrenic groups with low and with high rates. The possibility of laboratory error as a cause of the low rates is minimal, since the determinations in schizophrenic patients alternated with those made upon patients with multiple sclerosis.

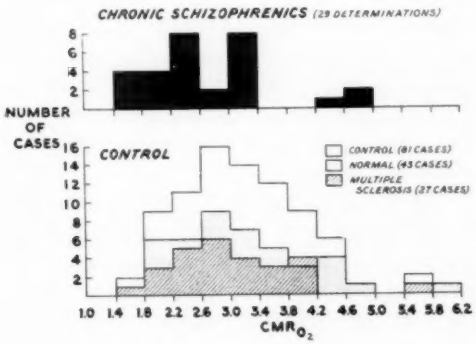
CHRONIC SCHIZOPHRENICS (29 DETERMINATIONS)
NUMBER OF CASES
CONTROL
CONTROL (81 CASES)
NORMAL (43 CASES)
MULTIPLE SCLEROSIS (37 CASES)
1.0 1.4 1.8 2.2 2.6 3.0 3.4 3.8 4.2 4.6 5.0 5.4 5.8 6.2
CMR$_{O_2}$

Figure 2

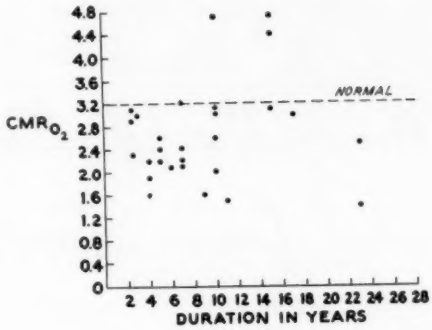

Figure 3

SUMMARY

The cerebral uptake of oxygen in 10 of 24 patients with chronic schizophrenic reactions of two or more years' duration was sufficiently low to make the CMR_{O_2} of the entire group significantly lower than normal. Low rates were found in patients whose disease had existed for four or more years. No other clinical feature could be correlated with low CMR_{O_2}. The late occurrence of the cerebral metabolic defect suggests that the low rates are secondary to the schizophrenic process or to its sequelae.

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Motor Effects of Lesions of Precentral Gyrus and of Lesions Sparing This Area in Monkey

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It is clear that cortical control of movement is not vested exclusively in the classic "motor area" of the precentral gyrus. Extrapyramidal corticifugal fibers originate from parietal, temporal, and occipital loci, as well as from all major parts of the frontal lobes.* Electrical stimulation of these regions may evoke adversive or synergic movements of the eyes, ears, head, trunk, and limbs.† Moreover, the pyramidal tract arises from a more extensive cortical region than was previously supposed. Lassek [9] has reported that ablation of Area 4 causes degeneration of only 27% to 40% of pyramidal fibers. Chromatolysis in the parietal lobe following spinal hemisection [10] indicates parietal components, which have received further confirmation in experiments employing antidromic stimulation of the pyramid.[11] Finally, degenerated fibers have been found in the pyramidal tract following parietal,[12] temporal, and occipital ablations.[13]

The functional significance of the dichotomy between pyramidal and extrapyramidal projections, or of that between so-called motor and other cortical areas, remains controversial. The pyramidal tract has been characterized as the pathway for fine, voluntary movements. Aside from the philosophical difficulties inherent in this usage, studies on monkeys after pyramidal section indicate that they do not behave as automata, and retain or recover most of their normal capacities.‡ Mettler [16] characterizes nonpyramidal mechanisms as providing the background, "the skeletal set and large muscle stance . . . for gross adjustment to a relatively large number of situations," on which the precise movements mediated by the pyramidal system are superimposed. However, Lashley [17] came to an opposite conclusion on the basis of a study of retention of motor habits after lesions of the precentral gyrus in monkeys. He says:

> A normal function of the stimulable cortex is to supply a substratum of facilitating impulses which act in some way to render the final common paths excitable by the more finely graduated impulses descending from the cortex by extrapyramidal paths and producing the finer shades of adaptive movement.

Denny-Brown [14] likewise rejects on empirical grounds the identification of the Rolandic motor system with phasic, as opposed to postural, components of motor organization and denies its exclusive domain over fine, discrete distal movements.

The course of recovery following abalation of the motor cortex in primates has been studied by numerous investigators, but agreement on the facts and interpretation is not general. The motor effects of lesions of other cortical regions are less thoroughly documented and even more obscure. Observation of the effects of ablating the precentral gyrus in one hemisphere and the greater part of the remainder of the cortex in the

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* References 1 through 6.

† References 7 and 8.

‡ References 14 and 15.

other hemisphere, leaving the precentral gyrus intact, appeared to us a promising approach to elucidation of the roles of these systems. Specifically, we asked the following questions: 1. What are the comparative effects of a unilateral lesion of the precentral gyrus, and a massive unilateral lesion sparing this area, when each of these lesions is made in otherwise intact brains? 2. What is the effect of a unilateral lesion of the precentral gyrus subsequent to a massive unilateral lesion of the other hemisphere in which the precentral gyrus is spared? 3. What is the effect of a massive unilateral lesion sparing the precentral gyrus subsequent to a lesion of the precentral gyrus of the other hemisphere?

METHODS

Five immature monkeys, their weights ranging from 2 to 3.5 kg., were used. Nos. 1, 2, and 4 were macaques (Macaca mulatta), and Nos. 3 and 5 were green monkeys (Cercopithecus aethiops sabaeus). Two types of extirpations were made, each animal having a restricted ablation in one hemisphere and a massive ablation in the other, with an interval of 4 to 10 weeks between operations. In the restricted lesion, the precentral gyrus (exclusive of the ventrolateral part representing the face) was removed, between the central fissure and an approximately parallel line tangent to the bend of the arcuate sulcus; in the massive lesion, the precentral gyrus was preserved, and attempt was made to remove the rest of the cortex of the hemisphere, with the exception of its ventral and medial surfaces. In two animals, the restricted operation was performed first; the three remaining had the massive lesion first. Surgery was carried out with pentobarbital (Nembutal) or thiopental sodium (Pentothal Sodium) anesthesia, with aseptic technique. The extirpations were made by aspiration, except that the frontal, temporal, and occipital poles were usually separated by a blunt spatula and removed in a block. In connection with the massive lesion, it was found advisable to give a transfusion of 50 cc. of whole blood (from another monkey donor) or of Intragel (5% gelatin solution), and to insert drains, which were left in place for two or three days, at the anterior and posterior ends of the incision.

After each operation, observations were made of the positions characteristically assumed, and of the use of the limbs in progression about the cage and in walking, running, and climbing within a large enclosure. Posture and preferential use of the hands in reaching and grasping were noted. Attempt was made to elicit placing and crossed placing reactions. During regular examination, the monkey was confined to a chair by a bar across the thighs and a projecting wooden frame around the neck. This arrangement permitted free movements of the limbs, while excluding vision of stimuli applied to the trunk or extremities. In the chair, reactions to palmar and plantar stimulation (by placing an object in contact, and by brisk stroking with a blunt-pointed instrument) and response to touch and pinprick were tested.

During the first week after operation, daily protocols were kept. Thereafter, observations were recorded every fourth or fifth day. After surgery on the second hemisphere, the period of observation varied from two weeks to three months in different animals. The dates of operation and killing the animal are given in the Table.

After the monkeys were killed, their brains were fixed and sectioned; reconstructions were made of the cortical excisions, and degeneration was studied in the thalamus. Histological procedures and method of reconstruction have been described elsewhere.[18]

Dates Operation Was Done and Animal Was Killed *

Subject	Operation 1	Operation 2	Time of Killing
1.....	3/10	5/23	8/2
2.....	3/23	6/9	6/24
3.....	5/24	6/21	7/1
4.....	5/29	6/26	9/24
5.....	5/31	6/29	7/23

* All work done in 1950.

RESULTS

Anatomical Data

Reconstructions of the cortical lesions, cross sections through the lesions, and pictures of thalamic degeneration in all subjects are shown in Figures 1, 2, and 3. Every eighth stained cross section through the cortex and every second stained section through the thalamus are presented. In general, the cortical lesions were comparable from animal to animal, with only minor variations. The two types of extirpation were not strictly complementary: The lesions of the precentral gyrus were narrower than the corresponding regions spared in the opposite hemisphere.

Degeneration in the thalamus did not entirely conform to Walker's [19] schema of the projection on the cortex of the various parts of the ventrolateral nuclear group. The lesion

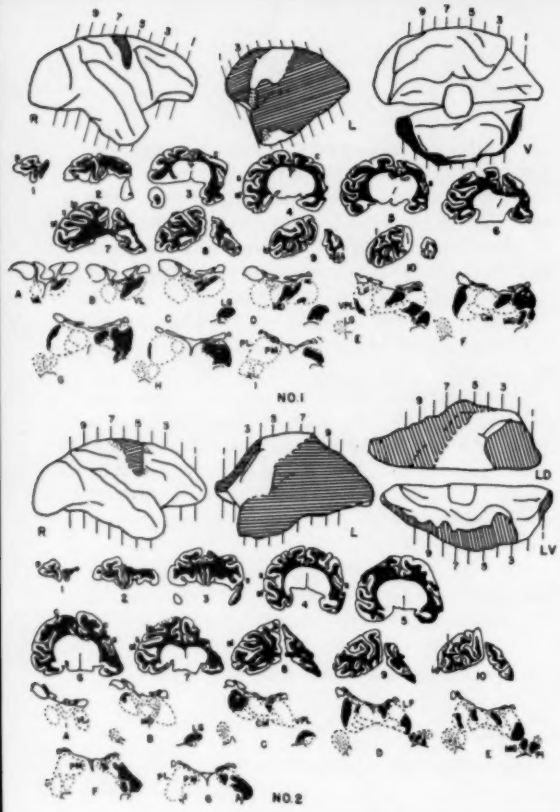


Fig. 1.—Record of lesions in Subjects 1 and 2. In this, and in the following reconstructions of cortical lesions, complete excision is indicated by hatching and partial destruction by stippling. Preservation of the depths of sulci is indicated by interrupted lines. The positions of the cross sections are shown by the numbered lines on the surface drawings. The cortical gray matter is represented in white in these cross sections. Sections through the thalamus, from anterior to posterior, are given. Definitely degenerated regions are shown in black; regions of "doubtful" degeneration [18] are stippled.

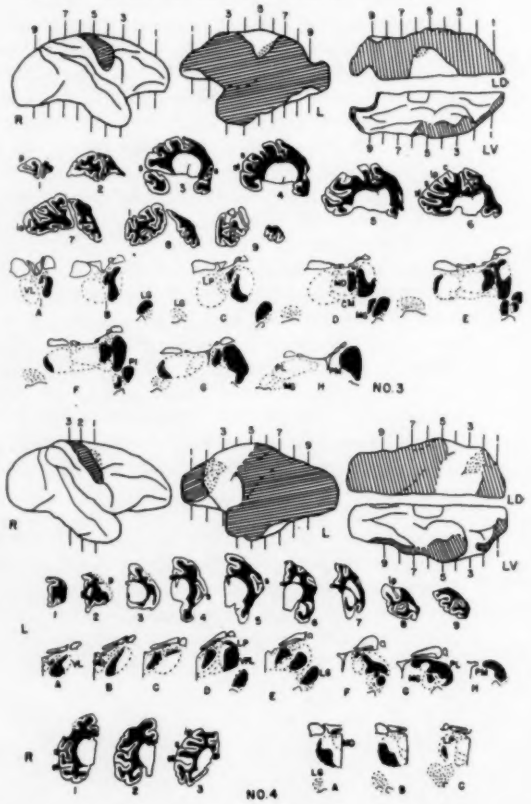
of the precentral gyrus in Nos. 1 and 3 left n. ventralis lateralis completely intact. This lesion, however, produced an area of degeneration in n. ventralis posterolateralis of all subjects and in n. lateralis posterior of four of the five subjects. On the contrary, the massive lesion which spared the precentral gyrus caused retrograde degeneration in n. ventralis lateralis in all cases (with the possible exception of No. 5, where degeneration in this nucleus was "doubtful"). It appears that, in some monkeys at least, the precentral gyrus receives its thalamic projection from the principal somatosensory nucleus, and that the projection from n. ventralis lateralis may terminate rostrad. Details of the cortical field receiving fibers from the ventrolateral nuclear group will be discussed fully in a later publication, in connection with a larger series of cases.

Behavioral Effects

Motor effects of the two types of ablation are presented below. First, we describe the effects of unilateral removal of the precentral gyrus; second, the effects of a massive lesion which spares this area. Next, we consider the changes produced by the quasicomplementary lesion in the second hemisphere, i. e., either a massive removal added to a previous contralateral ablation of the precentral gyrus, or, vice versa, removal of the precentral gyrus opposite a previous lesion sparing this area. Under each of these four headings, the results are further summarized in a series of stages: immediate effects of the operation (noted in the first five postoperative days), condition at the end of the second week, condition at the end of the first month, and condition at the end of the second month.

Removal of Precentral Gyrus Alone.—The precentral gyrus was removed from the

Fig. 2.—Record of lesions in Subjects 3 and 4.



right hemisphere of Subject No. 2 and from the left hemisphere of Subject No. 5. This operation produced effects on the contralateral limbs which included abnormal postures, greatly restricted and awkward use, failure to withdraw from noxious stimuli or to participate in defensive movements, and absence of contralateral placing reactions.

Immediate Effects: Trunk posture was grossly normal in both animals. In No. 2 the contralateral arm hung limp at the elbow, wrist, and digits, whereas in No. 5 the so-called "paretic posture" was observed, the elbow being semiflexed, adducted, and pronated, the wrist dropped, and the digits slightly curled. The contralateral leg of No. 2 was either loosely extended or held semiflexed at the knee, with adduction of the thigh and medial rotation of the lower leg. Leg posture was normal in No. 5.

The contralateral hand of No. 2 was never used for support and only rarely and feebly hooked on to the cage mesh. In No. 5, the hand was occasionally used for support as he turned, and could be hooked on to the cage wires in climbing. In both animals, the leg dragged behind in walking and climbing, and control of movement was defective. Neither animal used the contralateral hand in reaching for food, or for holding food to the mouth.

No. 2 did not grasp objects placed in the contralateral hand or foot; the grasp was weaker and less complete than normal in the contralateral hand of No. 5 and absent in his contralateral foot. Neither animal responded to brisk stroking of the plantar surface of the affected foot or to touch or pinprick on the contralateral limbs. The contralateral leg did not place or cross place, even when vision was permitted. The ipsilateral leg, however, showed both the placing and the crossed placing reactions.

Condition at End of Second Week: The resting postures of the two animals were now grossly similar. Both held the contralateral arm in partial flexion at elbow and wrist. The contralateral fingers of No. 5 were tightly clenched, however, whereas those of No. 2 continued to be loosely extended.

Walking and climbing had improved in both animals, but the opposite limbs were used less often, and less efficiently, than those on the same side as the lesion. The contralateral arm and leg frequently dragged, slipped, missed hold, and failed to execute movements of proper range and direction. The affected hand was still not used in feeding behavior.

No. 5 now failed to grasp objects in contact with the contralateral hand, as well as with the contralateral foot. No. 2 continued to be unreactive to such stimuli. Only relatively intense or repeated tactile or painful stimuli on the contralateral side elicited defensive movements. These movements were made only with the ipsilateral hand or foot;

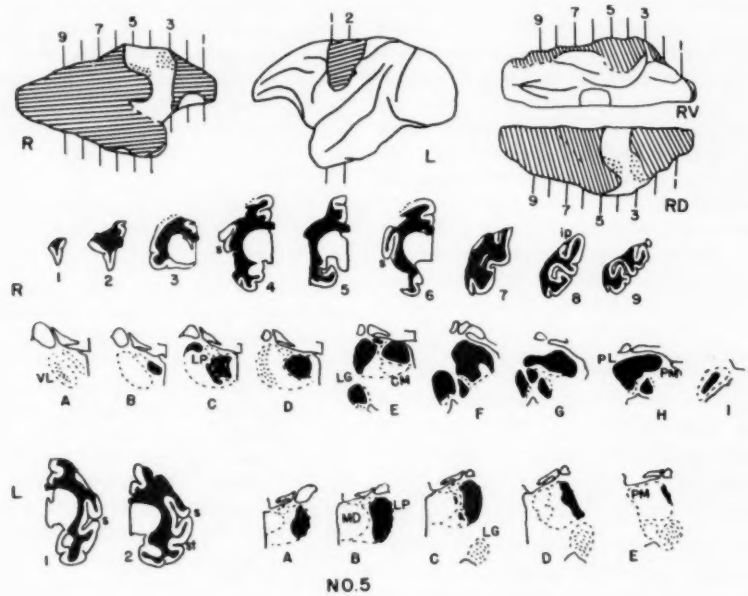


Fig. 3.—Record of lesions in Subject 5.

no such movements could be obtained from the other limbs, even when the ipsilateral ones were restrained. The response to plantar stimulation continued to be absent. Placing remained as previously described.

Condition at End of First Month: Posture of the limbs was now approximately normal. Their use in locomotion, whereas further improved, was still noticeably restricted and awkward. Both animals had begun to use the contralateral hand in supporting large pieces of food at the mouth, but this hand was not used in reaching for objects, or in grasping them when they were placed in contact.

Neither animal responded to stroking of the contralateral sole. There was now no evidence of reduced sensitivity to touch or pinprick on the contralateral side, but the response to stimulation was still abnormal, in that there was no specific withdrawal of the member concerned and no attempt to ward off the noxious agent except with the ipsilateral limbs. The contralateral foot still did not place under any conditions of stimulation.

The second operation on No. 5 was performed at this time.

Condition at End of Second Month: The locomotor disabilities of No. 2 were gradually lessening. Objects placed in his contralateral hand were now weakly grasped. Otherwise, his condition was unchanged.

Massive Unilateral Removal Sparing Precentral Gyrus.—This lesion was made in the left hemispheres of Nos. 1, 3, and 4. Trunk posture was affected, as well as posture of the contralateral limbs. These limbs were rarely used, and their movements were ill-coordinated and dysmetric. These abnormalities gradually abated. Diminished somatosensory sensitivity persisted in some degree for as long as the animals were observed. The placing and crossed placing reactions of the contralateral limbs remained absent. The ipsilateral limbs placed in response to direct contact, but did not respond following stimulation of the opposite member.

Immediate Effects: Nos. 1 and 3 were semiprostrate for two days after operation. They occasionally struggled to get up or to crawl on their bellies with the help of the ipsilateral limbs. No. 4, in which there had been replacement of blood loss during the operation, was sitting up and eating unaided the following morning. In all animals, the trunk was flexed in sitting, although the head was held fairly erect. The contralateral limbs tended to be loosely extended, although sometimes they assumed a half-flexed position. The hemiplegia was more profound in Nos. 1 and 3, but less profound in No. 4, than in the animals from which the precentral gyrus had been removed. Facial hemiparesis was present in No. 1.

The contralateral limbs were rarely used even for support and tended to be dragged behind and to assume unusual postures as the animals moved about their cages. Gait was ataxic: The animals staggered, overstepped, and had difficulty in maintaining balance. In spite of these handicaps, there was mild hyperactivity, with circling toward the side of the lesion. The contralateral hand was not used in feeding behavior.

There was no grasp of objects placed in the contralateral hand or foot, and no reaction to stroking of the contralateral plantar surface. None of the subjects responded to sensory stimuli applied to the side of the body opposite the lesion (except that No. 4 withdrew from pinching in the first few hours after operation, although not subsequently). The placing reaction could not be obtained with the contralateral leg, and there was no crossed placing with either extremity.

Condition at End of Second Week: Limb posture was grossly normal in all animals, but the back was still markedly bent over.

Use of the limbs was much improved in Nos. 1 and 4, less so in No. 3. In all animals, the leg appeared more nearly normal than the arm, although locomotion was still somewhat ataxic, with exaggeration of normal stepping movements on the contralateral side. In climbing, No. 3 hardly ever used the contralateral hand or arm; No. 4 used it less than normally and tended to slip and lose hold with it; No. 1 used the arm almost as much as normally, but it was sometimes noted that he hooked the forearm around the cage wires instead of using the fingers. Except in No. 3, the hand was now employed in holding food to the mouth, but was not used in reaching for and grasping food morsels.

Contact with objects did not elicit grasping with the contralateral hand or foot. There was no response to plantar stroking, except in No. 4, who showed a weak withdrawal. To obtain response to touch or pinprick, it was necessary to employ repeated or intense stimuli. Placing was absent, as previously described.

Condition at End of First Month: Trunk posture was now normal, or nearly so. Locomotion continued to be clumsy, but had improved in all animals. Walking appeared grossly normal in Nos. 1 and 4, but when they were running quickly, they tended to lurch and lose balance. In No. 3, disuse of the contralateral hand was obvious in feeding behavior and in ordinary walking. A similar abnormality could be brought out in the other two subjects under stress; for example, if the examiner held them by the loose skin at the back of the neck as

they walked. Nos. 1 and 4 would occasionally use the contralateral hand to peel back the skin of a banana, but the manipulations were coarse and inaccurate. When they held food to the mouth with this hand, the piece was supported rather than grasped, the digits being slightly curled underneath the object instead of around it.

Response to palmar contact and to plantar stroking was absent in Nos. 1 and 3. No. 4 grasped in response to contact, but the position of the digits tended to be maintained after the object was removed. Plantar stroking elicited weak withdrawal in No. 4. Sensitivity to touch and pinprick was demonstrable in all animals, but was still diminished contralaterally. In No. 3, there appeared to be difficulty in localization on the contralateral side: His hand would move in the direction of the stimulated spot but would stop several inches away. Placing remained absent, as previously described.

The second operations on Nos. 3 and 4 were performed at this time.

Condition at End of Second Month: No difference between the two sides of No. 1 could be detected in posture, locomotion, or feeding behavior. Residual defects were the contralateral facial paresis, diminished sensitivity to touch and pinprick on the contralateral limbs, failure to grasp an object in contact with the contralateral foot, weak response to brisk stroking of the contralateral sole, absence of placing and crossed placing reactions of the contralateral leg, and absence of crossed placing of the ipsilateral leg (in response to contact with the contralateral one).

Removal of Precentral Gyrus Subsequent to Massive Contralateral Lesion Sparing This Area.—The effects of removal of the precentral gyrus in the hemisphere opposite the previous massive removal of cortex other than the precentral gyrus in Nos. 1, 3, and 4 are described in this section. Here the term "contralateral" refers to the side opposite the more recent operation (ablation of the precentral gyrus); "ipsilateral" refers to the side opposite the previous massive lesion anterior and posterior to the motor regions proper.

Unilateral removal of the precentral gyrus produced contralateral effects which were qualitatively similar to those following this lesion in an otherwise intact brain. However, these effects were less pronounced and the animals recovered more rapidly.

On the ipsilateral side, some of the defects which had appeared following the massive removal (and from which the subjects had partially or completely recovered) were reinstated. These defects were again attenuated with the passage of time. In one case (No. 3), the ability to grasp objects in contact with the ipsilateral limbs was restored by the second removal.

Immediate Effects: In all animals, sitting posture reverted to the condition immediately following the initial massive removal: The trunk was not held erect, but was bent over. The limbs were generally held in a position of partial extension, or, less frequently, in semiflexion. No. 3 showed occasional epileptiform twitching of the contralateral hallux.

Nos. 1 and 4 used all four limbs weakly and uncertainly for support in standing and in locomotion. No. 1 used only the ipsilateral hand for reaching, although both hands participated in feeding behavior. No. 4 ate directly off the floor, without using either hand. Occasionally he would poke at the food with the ipsilateral hand. No. 3 could not walk or climb: He crawled with the contralateral leg dragging behind. When he turned, this leg was maximally flexed and used as a pivot. The ipsilateral hand was preferred and used in a slow, awkward manner, with gross dysmetria, but he rarely used either hand.

Objects in contact with the contralateral extremities of Nos. 1 and 4 were not grasped: No. 4 grasped only with the ipsilateral extremities, and No. 1, only with the ipsilateral hand. It is notable that No. 3 would now grasp with any limb, whereas before the second operation he had failed to grasp objects in the palm or sole opposite the massive lesion.

There was no response to touch or pinprick on either side in No. 4. No. 1 was responsive on the trunk, but sensitivity appeared to be diminished on the contralateral side. On the first day following operation, No. 3 was responsive all over to such stimuli; later, however, he did not respond when the contralateral leg or ipsilateral arm was touched or pricked. None of the three animals placed with either limb, regardless of whether contact was ipsilateral or contralateral, even when vision was permitted.

No. 3 was killed 10 days after the second operation.

Condition at End of Second Week: Trunk and limb posture were now normal in Nos. 1 and 4. In walking and climbing, the ipsilateral limbs of No. 1 and the contralateral limbs of No. 4 appeared more disabled. Use of the ipsilateral, as well as of the contralateral, hand had been diminished in both animals by removal of the precentral gyrus. Both now preferred the contralateral hand for reaching, although No. 4 had great difficulty in making con-

tact with a piece of food, in picking it up, and in getting it to his mouth with either hand.

A weak grasp could now be elicited in the contralateral hand of both subjects, and also in the ipsilateral foot of No. 1. Neither subject grasped objects with the contralateral foot. There was no response on either side to plantar stroking. Sensory status remained as previously described.

No. 1 now placed with the contralateral leg to direct contact stimuli, without vision. There was no crossed placing with this leg, however, and no placing or crossed placing with the ipsilateral leg. Placing remained entirely absent in No. 4.

Condition at End of First Month: Abnormalities on both sides, particularly in the lower extremities, were still evident in the locomotion of both subjects. The legs assumed an awkward, hyperextended posture, and tended to drag in walking. The ipsilateral leg of No. 4 was less efficient than the contralateral one in climbing, but little difference between the sides could be noted in No. 1. Both animals preferred the contralateral hand for picking up food but used either hand in holding it to the mouth. Neither hand was used with normal facility; the contralateral hand, however, was the better coordinated of the two.

Both animals grasped objects placed in contact with the hands or with the ipsilateral foot, but did not grasp with the contralateral foot. Plantar stroking elicited no response in No. 1; in No. 4, both sides were responsive, although stronger stimulation was required ipsilaterally. Sensitivity to touch and prick likewise appeared to be diminished on the ipsilateral side, although it was normal contralaterally. Placing remained as reported in the preceding section.

Condition at End of Second Month: Locomotion was grossly normal in No. 1. No. 4 showed some disability of the ipsilateral arm and leg when climbing and slight dragging of both legs in walking. Recovery of use and dexterity of the hands had also proceeded more rapidly in No. 1: In feeding behavior, he now used both hands with fair accuracy, whereas No. 4 showed past pointing and weakness of the ipsilateral hand and imperfect ability to close the contralateral fingers around an object. Preference for the contralateral hand persisted in both animals.

All four extremities of No. 1 would grasp objects in contact, but the contralateral foot of No. 4 was still unresponsive to such stimuli. Both animals now withdrew from plantar stroking on either side. In both, sensation still appeared to be subnormal on the ipsilateral side. Placing to direct contact stimuli, without vision, could now be demonstrated on the contralateral side in both. This limb did not cross place, however, and the ipsilateral leg neither placed nor cross placed.

No. 1 was killed during the following month.

Condition at End of Third Month: Residual abnormalities in No. 4 were confined to the ipsilateral side, with the exception of imperfect closure of the contralateral hand around objects. The ipsilateral hand was used less often and less efficiently than the contralateral one, and the ipsilateral leg dragged in locomotion. Placing remained as previously described.

Massive Unilateral Lesion Sparing Precentral Gyrus Subsequent to Contralateral Removal of Precentral Gyrus.—In this section, the effects of a massive lesion on Subjects No. 2 and No. 5 are described. These animals had previously been subjected to unilateral removal of the precentral gyrus of the opposite hemisphere, the sequelae of which are described above. Usage of the terms "contralateral" and "ipsilateral" is analogous to that followed in the preceding section. "Contralateral" designates the side opposite the more recent operation (in Nos. 2 and 5, the massive lesion sparing the posterior frontal lobe); "ipsilateral" thus means the side opposite the removal of motor cortex.

Our observations on the effects of this sequence of lesions are incomplete because the poor general condition of the subjects made it necessary to kill them in the course of the first month after the second operation. Nevertheless, these relatively short-term effects are of sufficient interest to warrant their inclusion.

No. 5 remained prostrate after this operation. At autopsy, it was found that much of the brain was softened. His protocol is included because the second operation ameliorated some of the deleterious effects which had resulted from the initial precentral ablation. On the side opposite the earlier removal of the motor cortex, the hand and foot now grasped objects in contact; the foot withdrew from plantar stroking and exhibited the contact-placing reaction. These effects were noted on the day after operation when he was first tested.

In No. 2, the contralateral effects of the second operation were similar in some respects to those following this lesion in an

otherwise intact brain. Some of the expected defects did not occur, however: There were no effects on posture of the limbs, or on grasping, or on limb withdrawal from plantar stimulation. On the ipsilateral side, some of the abnormalities which had followed the initial ablation of the precentral gyrus (and from which he had shown recovery) were reinstated: The upper limb again assumed the "paretic posture," and the use of both limbs was worsened. Other effects were the immediate, or very rapid, amelioration of some of the disabilities which had persisted until the second operation: The limbs withdrew from somatosensory stimulation, and the placing and crossed placing reactions reappeared in response to appropriate tactual stimulation.

Immediate Effects: Trunk posture in No. 2 showed hypotonia of the extensors, a characteristic effect of the massive lesion. The position of the contralateral limbs was normal, but the ipsilateral arm again showed the "paretic posture." No. 5 was prostrate. The contralateral arm was held in maximal internal rotation, with elbow and wrist flexed and fingers extended. The contralateral leg and both ipsilateral members were partially extended.

Movements of the contralateral limbs were slow and inaccurate in No. 2 and completely absent in No. 5. Both subjects showed renewed impairment of the ability to use the ipsilateral limbs. No. 2 occasionally circled toward the side of the recent lesion.

The massive lesion sparing the precentral gyrus produced no alteration of grasping reactions in No. 2: Objects placed in contact were grasped with either hand, but the response was absent in the ipsilateral foot. In contrast, this lesion affected grasp in No. 5 on both sides. Grasping was now absent contralaterally, but had reappeared on the ipsilateral side.

There was no response to touch or pinprick on either side in No. 2. No. 5 did not respond to such stimulation of the contralateral side, but ipsilateral stimuli remained effective. Either limb of No. 2 withdrew from stroking of the plantar surface. The contralateral foot of No. 5 did not withdraw, but a weak response had reappeared on the ipsilateral side.

A striking change was that both subjects now exhibited contact placing with the ipsilateral foot, vision being excluded. No. 2 also cross placed with this limb to stimulation of the opposite member. No placing on the contralateral side could be elicited in either subject. These reactions had been absent immediately before the second operation.

Condition at End of Second Week: In No. 2, the trunk was still somewhat bent over, and the ipsilateral arm was still held in the semiflexed position. No. 5 remained prostate. The contralateral limbs were held in flexion, the ipsilateral ones in extension, regardless of the side on which he was lying. It was difficult to alter the position of any limb forcibly.

Slight hyperactivity persisted in No. 2. In locomotion, the ipsilateral arm and leg often dragged behind. These limbs were not used as much as the contralateral ones. He preferred the contralateral hand for reaching food and holding on to the cage wires. Contralateral movements of reaching and grasping were now more accurate than ipsilateral ones. Occasionally, he used the ipsilateral hand in scratching or in an unsuccessful attempt to pick up a piece of food.

Grasping to contact stimuli was as previously described. There was no response to touch anywhere in either animal, or to pinprick in No. 5. Pinprick on the contralateral side of No. 2 elicited vocalization, but no withdrawal; the ipsilateral limbs withdrew from prick. A response to plantar stimulation could be obtained from either limb of No. 2, but whereas the response on the ipsilateral side was dorsiflexion of the foot, there was gross withdrawal of the entire contralateral limb. No. 5 no longer responded to plantar stroking. Placing reactions could no longer be elicited in either subject.

The general condition of both animals was now poor. No. 2 had developed severe dysentery. Medication was ineffective; so it was decided to kill him. In the following two weeks, the condition of No. 5 became worse. The limbs developed contractures. He became unable to retain food. He was killed nearly a month after the second operation.

COMMENT

Comparison of Effects of Lesions of Precentral Gyrus and of Lesions Sparing This Area.—Unilateral lesion of the precentral gyrus (with the opposite hemisphere intact) produced contralateral effects which included abnormal postures, mainly of the upper limb; relative disuse and lack of dexterity; failure to grasp objects in contact with hand or foot; diminished sensitivity to somatosensory stimuli; failure to withdraw or make defensive movements with the affected limbs in response to tactile or painful stimulation, and absence of the placing and crossed plac-

ing reactions. At the end of the first postoperative month, sensitivity no longer appeared to be diminished, but recovery was not complete from many of the other defects. During the second postoperative month, only posture returned to normal. The other abnormalities persisted, although some became attenuated.

The massive lesion sparing the precentral gyrus (with the opposite hemisphere intact) likewise produced all these effects, with the exception of the flexed posture of the joints of the upper limb, and with the addition of effects on trunk posture. Although the defects produced were in general similar, their duration differed. The apparent diminution of sensation persisted for as long as the animals were observed, whereas the recovery of normal contralateral limb posture, of use and dexterity, and of specific withdrawal and defensive movements proceeded more rapidly than after lesion of the precentral gyrus.

The difference in the effects of these lesions, for most of the functions tested, thus appears to be better described as quantitative rather than qualitative. These results perhaps reflect the lack of clear anatomic separation of pyramidal and extrapyramidal systems at the cortical level. Moreover, the greater effect of ablation of the precentral gyrus on both phasic and postural components of motor behavior does not support the functional distinction usually made between these systems.

The evidence indicates that much of the deficit resulting from ablation of the precentral gyrus is neither sensory nor motor in a strict sense. In our animals with this lesion, the persisting failure of the contralateral limbs to withdraw from somatosensory stimulation, or to engage in attempts to ward off the stimulus, is a case in point. The specific movements they failed to make in this situation were not different from those they commonly made in ordinary progression about their cages. Appropriate substitutive movements with the ipsilateral limbs showed that the stimuli were felt. As Denny-Brown [14] has emphasized, the result of lesions of the motor area is that certain stimuli become inadequate to elicit the normal motor response.

Effects of Removal of Precentral Gyrus Subsequent to Massive Contralateral Lesion Sparing this Area.—We have discussed the effects of unilateral lesion of the precentral gyrus in an otherwise intact brain. If, however, this lesion is made in a brain with extensive destruction in the other hemisphere, the effects contralateral to the precentral ablation are less severe and enduring. In all the functions tested, recovery took place more rapidly. Amelioration of defects referable to the latter of two bilateral seriatim lesions has been reported by Lashley [17] and by Ades and Raab.[20] In both of these experiments, the operations were symmetrical removals of the motor areas. The similarity of effect when the initial lesion is outside the motor area proper is additional evidence of the qualitative equivalence of the precentral gyrus and extra precentral cortex. The exacerbation of defects on the side contralateral to the initial lesion likewise suggests that compensatory relations may exist between heterotopic regions of the hemispheres.

Effects of Massive Lesion Sparing Precentral Gyrus Subsequent to Contralateral Removal of Precentral Gyrus.—The contralateral effects of the massive lesion, when it was the second of the seriatim operations, appeared to be less than when this lesion was made initially. Although our data are limited by the short survival time of the animals in which this sequence of lesions was made, it was clear that, under these circumstances, the massive lesion may have no effects on contralateral limb posture, grasping, response to plantar stimulation, and the afferent basis of the placing reaction. Thus, with either sequence of lesions, the initial ablation must effect a partial change in the neural mechanisms underlying functions of the limbs ipsilateral, as well as contralateral, to it.

The ipsilateral effects of these unilateral lesions become directly observable when either is made in the intact hemisphere of an animal which has the quasicomplementary

removal on the opposite side. We have mentioned that the effect of the removal of the precentral gyrus, when it followed the massive lesion, was predominantly to exacerbate abnormalities which had resulted from the initial operation. Although the massive lesion, when it was the second of the series, likewise caused renewal of defects (in posture and dexterity), there were in addition numerous ameliorative effects on the disturbed functions of the limbs ipsilateral to it. These effects (restoration of grasping, of specific withdrawal from stimulation, and of the contact placing reaction) were noted on the day following operation, when the animals were first tested. The nature and rapidity of these changes make it unlikely that a process of relearning was involved in recovery.

Qualitative differences between lesions of precentral gyrus and of other cortex thus are more prominent in their ipsilateral rather than in their contralateral effects. Perhaps these results also point to a factor underlying the more lasting disabilities induced by the precentral ablation as compared with the lesion sparing this area, when either of these removals is made in an otherwise intact brain. The presence of the contralateral cortex outside the precentral motor area appears in some way to hinder reorganization of certain functions after ablation of the precentral gyrus. With regard to other abilities, this extra-precentral area may directly or indirectly play a positive role in the restitutive process.

General Comment.—The results of these experiments indicate a far more dynamic cortical organization of motor function than that generally held. The simple distinctions of "pyramidal" and "extrapyramidal," and of "motor" and "sensory," are clearly inadequate to describe the data. Rigid anatomico-functional schemata do not readily encompass the similarity of effect of lesions of the precentral gyrus and of lesions which spare this area; the less severe contralateral effects of either operation (precentral or extraprecentral) if preceded by the other; the exacerbation or amelioration of defects, initially referable to the massive lesion sparing the precentral gyrus, depending on whether the contralateral precentral operation followed or preceded it, and the immediate, or very rapid, amelioration by the later massive lesion of certain abnormalities which had persisted since the earlier removal of the precentral gyrus. These results suggest a complicated interaction between the two hemispheres and a plasticity of function rarely envisaged in existing theories. They further emphasize the limitations of the ablation experiment and the caution that must be exercised in concluding that a given structure is necessary to a certain item of behavior because the item is "permanently" absent following removal of the structure.

SUMMARY

The effects of unilateral ablation of the precentral gyrus and those of a massive lesion sparing this area were compared in monkeys. On most of the items of behavior observed, the contralateral abnormalities produced by these removals were similar. The duration of effect differed, however.

After an interval of 4 to 10 weeks, the monkeys with ablation of the precentral gyrus were subjected to the massive lesion in the opposite hemisphere, and vice versa. The effects of each of these lesions on the side of the body contralateral to it were less severe than those following the same lesion in an otherwise intact brain.

On the side of the body contralateral to the initial massive lesion, the principal effects of subsequent ablation of the precentral gyrus was to reinstate defects from which the animals had partially or completely recovered. After the reverse sequence of lesions, certain abnormalities on the side contralateral to the initial removal of the precentral gyrus were likewise renewed; in addition, there was immediate, or very rapid, amelioration of many of the defects which had persisted since the first operation.

Some implications of these results for theory and experiment are discussed.

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Drug Addiction in the Involutional Period

Report of Four Cases

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In four years' experience * with narcotic addicts we have become aware of a particular clinical picture involving drug addiction which seems of sufficient significance and interest from a theoretical and practical standpoint to warrant a short preliminary report.

Among those patients routinely admitted to this hospital for the treatment of drug addiction, a certain number have been observed to have the following history and clinical characteristics: These patients, generally men in our experience, are in the involutional age group and have previously made a reasonably acceptable professional or semiprofessional adjustment with satisfactory sustaining interpersonal relationships. Following certain traumatic emotional experiences, in some way involving disruption of this previous pattern, a depressive reaction occurs in which the usual psychological symptoms and physiological concomitants of depression are seen. In the course of development of this clinical picture these persons encounter drugs, generally fortuitously, and utilize them as a defense against their anxiety and depression, often masking the depressive features. The duration of the drug usage is generally brief but may involve the use of alcohol and the barbiturates, as well as the opiates. The presenting complaint, then, is that of drug addiction; however, as withdrawal from narcotics is effected, the underlying depression is revealed. Often this is further masked by various somatic complaints or depressive equivalents.[1] Dynamically, it becomes apparent that the depression is the primary difficulty and the use of drugs has been a way of relieving the concomitant anxiety. The depression and anxiety, once recognized, will often respond satisfactorily to electric shock therapy or subcoma insulin treatment. Of equal importance, therapeutically, is a sustaining relationship with the psychiatrist directed toward the reestablishment of meaningful interpersonal relationships.

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REPORT OF CASES

CASE 1.—This 65-year-old white man, a retired mortician, was admitted to the hospital voluntarily for the treatment of addiction. His original use of drugs occurred in 1931, after the death of his first wife, and continued sporadically until 1939. At that time he returned again actively to his business affairs and made a seemingly adequate adjustment until 1945. He had always been a competent business man and had achieved a respected place in the community through his philanthropic and community activities. By 1945, however, he began to exhibit defects in memory, concentration, etc., that impaired his ability to handle business affairs, and it became necessary for his son to take over. Depressed moods occurred, and the patient frequently verbalized feelings of guilt and inadequacy, superficially related to his waning capacities. Although he had remarried, this relationship was not sufficient to sustain him, and he was unable to become interested in other diversionary activities. He began to use drugs again, and in the ensuing few years had several short periods of hospitalization for this. These were not successful, as efforts were chiefly directed toward blocking his sources of supply of drugs rather than toward management of the basic problem.

Just prior to admission here, he had been using barbiturates chiefly, and these were uneventfully withdrawn, revealing the rather deep-seated underlying depression. A course of electric shock therapy was contemplated, but the patient decided to leave the hospital. Some insight was given the family as

to the basic problem, with the recommendation that future management be chiefly directed toward specific treatment of the depression.

CASE 2.—This 42-year-old white civil engineer was admitted on sentence for a narcotic violation resulting from use of barbiturates and small quantities of opiates, accompanied by excessive alcoholism, existent for approximately one year. Onset of this pattern followed a previously adequate work and social adjustment. He had been married about 20 years, with a seemingly harmonious relationship with his wife. The present illness was precipitated by several factors, chiefly business reverses, unexpected financial obligations connected with his wife's hospitalization and surgery, and, more important, the sudden, and to him inexplicable, change in his relationship with his wife following her operation. This relationship deteriorated rapidly and culminated in divorce, with his wife soon remarying a man entirely unknown to him. At this point he began drinking heavily and used barbiturates and opiates, which further adversely affected his social and business adjustment and his relationship with his family. During this period he made several attempts to avoid the use of drugs or alcohol and to reestablish himself in productive work. Each time he became overwhelmed by feelings of guilt, worthlessness, and remorse and reverted to the use of opiates, barbiturates, and alcohol. On several occasions while oversedated or heavily narcotized, he was involved in automobile accidents, which might have been interpreted as unconscious suicidal gestures. Ultimately, he violated a narcotic law and was sentenced here. Coincident with the trial and sentence, his wife indicated her feeling that she had made a mistake in leaving him, and her desire to effect a reconciliation with him, extending the hope that perhaps after his release they could resume their former relationship. This hope was of tremendous psychological importance to the patient, alleviating his feeling of hopelessness and dissipating the depression against which he had been defending himself by the use of alcohol and drugs.

CASE 3.—This 55-year-old white physician was admitted voluntarily for the treatment of addiction. He had been using relatively small quantities of opiates, mostly codeine, for five to six years, the emotional aspects of his dependency upon them being predominant. His use of drugs was related to a depressive reaction following the death of his wife after 20 years of marriage. There had been no children, and the most distressing implication of her death to him was that "she left me all alone." He was discharged from the Navy at that time, but his attempts to reestablish himself in practice on the same successful basis he had enjoyed in the past were interfered with by his depression, manifested by disturbances in physiological functions of appetite and sleep, depressed mood, crying spells, and feelings of guilt, remorse, and unworthiness. More or less fortuitously at this time, he found that small doses of opiates would relieve his depression, replacing it with a feeling of euphoria, enabling him to carry on his activities in a more normal fashion. Although he recognized he was depressed and that he was using the opiates as a stimulant, his entire orientation and that of his friends and physicians was that his use of the drugs was the significant factor, and the presence of the underlying depression was overlooked or neglected. This contributed to the fact that several previous attempts to "cure" his addiction were unsuccessful. Following admission here, and withdrawal from opiates, which was readily accomplished, the depression became obvious and a course of electric shock therapy was instituted. The problem of reinstating meaningful, sustaining interpersonal relationships in the home situation remained to be handled following discharge.

CASE 4.—This 51-year-old, recently widowed rancher was admitted to the hospital voluntarily, seeking treatment for addiction to dihydromorphinone (Dilaudid) and meperidine (Demerol). His use of narcotics was of approximately two years' duration, and prior to that time he had apparently been eminently successful as a farmer and rancher. The patient related the onset of his addiction to a series of physical illnesses, as well as to the emotional turmoil he experienced in caring for his wife during a terminal illness. Opiates had apparently been prescribed for relief of pain associated with phlebothrombosis, a complication from an operation for supposed obstruction of the descending colon. Approximately 10 months prior to the patient's admission to the hospital he learned that his wife had carcinoma of the uterus, and when other forms of therapy failed, she was apparently deliberately addicted to dihydromorphinone and meperidine in order to afford relief from pain. Prior to her death, a month before the patient was admitted, he claims that he nursed her night and day and that during this time he, himself, used some of her medication.

After his admission to the hospital the patient was evaluated from a medical and psychiatric standpoint. He continued to experience pain and discomfort in the legs because of thrombosis of the veins, and a GI series revealed a duodenal ulcer. It was apparent, however, that the patient was also suffering from a fairly severe depression, as evidenced by a suicidal attempt, episodes of crying, and the expression of self-depreciatory ideas. After withdrawal from narcotics and some stabilization of his physical condition, the patient was placed on subcoma insulin treatment, as a result of which he evidenced considerable improvement. It was believed however, that electric shock treatment was indicated, but this proposal was too threatening to the

patient, and he left the hospital, against medical advice, before the treatment could be instituted.

COMMENT

An important consideration involved in the presentation of this group of cases was the fact that further differentiation of various groups of drug addiction patients might clarify some of the misconceptions about drug addiction and the drug addict. This group is just one segment of the total group of patients who use drugs to excess, but its delineation is of importance for two reasons. First, it is an attempt to amplify the concept of diversity among drug users,† and, second, many such patients, because of the superficial presenting complaint of addiction, may be misevaluated, with the result that an effective treatment approach is neglected. This problem is further complicated by the fact that the somatic symptoms of depression may serve as the patient's rationalization for the use of drugs.

That this group can be differentiated is not a unique circumstance, as it would appear that other groups with similar implications as to treatment and management approach can also be differentiated. For example, certain schizophrenics utilize drugs for relief of anxiety and tension. The problem then superficially appears to be that of drug addiction; however, after withdrawal the underlying schizophrenic adjustment and symptomatology are generally readily seen.

† References 2 through 5.

SUMMARY

1. An attempt is made to clarify the clinical picture of drug addiction complicating and masking what is essentially a depressive reaction within the involutional period.

2. Case histories are cited.

3. Some consideration is given to the value of considering the specific characteristics of certain groups of drug addicts for the purpose of developing a more meaningful concept of drug addiction.

4. The specific treatment implications of one such group are indicated.

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The Analeptic Action of Peripheral Electrical Stimulation in Insulin Coma

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It has been reported by Hoffman and Wunsch [1] and Riboli [2] that electrical stimulation applied to the head will arouse patients from hypoglycemic coma. Whereas Hoffman and Wunsch applied a pulsating direct current in the nonconvulsive method of Hirschfeld,* Riboli used a prolonged administration of low-voltage alternating current of 50 to 80 ma. These workers suggested that the return to consciousness was due to diencephalic stimulation by transcerebrally directed current. This transcerebral-diencephalic stimulation theory is commonly mentioned in reports on nonconvulsive electroshock therapy and reports on the treatment of barbiturate coma by nonconvulsive techniques.† With respect to barbiturate-induced coma this hypothesis has been seriously challenged by Blachly and Brookhart.[5] These investigators have found that the respiratory augmentation accompanying electrical stimulation can be ascribed solely to the activation of afferent nerves and that direct stimulation of the brain is not an essential element in the production of the response. It was further observed in barbiturate-depressed dogs that electrical stimulation of the legs produced respiratory responses and behavioral arousal which were identical to those produced by stimulation through the head. It is therefore necessary to consider seriously the possibility that the results of certain forms of cranial stimulation may be due primarily to the impingement of massive barrages of afferent impulses upon the central nervous system, rather than to the direct excitation of the brain by the electrical current.

In the light of these considerations, we have attempted to determine whether peripheral electrical stimulation will also influence the course of insulin-induced coma.

METHOD AND MATERIALS

Two schizophrenic patients who were completing therapeutic series of 50 coma hours were first selected and were awakened by peripheral electrical stimulation on each of five trials. Five additional schizophrenic patients were chosen whose patterns of response to insulin were also well known and who had no history of spontaneous awakenings. In this latter group, blood samples for glucose determinations (Folin-Wu method) were taken before insulin was injected, at the onset of coma, immediately prior to electrical stimulation, and immediately after the patients awakened. The onset of coma was determined by the criteria of Himwich[6] for the subcorticodiencephalic phase, which is characterized by loss of environmental contact and the various motor, sensory, and autonomic manifestations of release of the subcorticodiencephalon. Two trials, a week or more apart, were made on each patient—one early or midway through the coma, and the other near the end, when glucose would have otherwise been given. The point of awakening was determined as that at which the patients responded to simple questions and recognized and named personnel members of the insulin

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† References 3 and 4.

room. Electrical stimulation was provided by a Reiter Electrostimulator Model CW-47. A 3×5 in., saline-soaked asbestos electrode was placed over the anteromedial aspect of each lower leg and attached by a Y-connection to the negative outlet of the stimulator. A third electrode, 3½×10 in., was placed over the lumbosacral region and connected to the positive outlet. The current delivered from position I of the machine was applied in the manner developed here for therapeutic purposes. With this method, the current was gradually increased to the point where maximum clonic movements of the lower extremities were obtained. This generally required from 5 to 15 ma. Care was exercised to avoid current intensities capable of producing prolonged tonic extension of the limbs. Current was maintained at the optimum level until the patient began to struggle, and was gradually lowered as the patient's tolerance decreased. During the last five minutes of each treatment, polarity was reversed at frequent intervals, usually about every minute. After the patients had awakened, they were given dextrose to avoid a possible return of coma and the complications of prolonged hypoglycemia which frequently occur in comas of more than one hour.

RESULTS

In each of the 15 trials peripheral electrical stimulation succeeded in arousing the patient from hypoglycemic coma. The pattern of response was identical in each case. With the onset of stimulation, each patient showed an increase in the rate and volume of respiration, and there was a marked dilatation of pupils. Usually, about five minutes before awakening, the patient moaned, raised his arms, or perhaps withdrew a leg to a slight degree. At this point changing polarity caused the patient to increase these efforts, and, likewise, increasing the current caused more vigorous struggling movements. Often the head and shoulders were lifted off the pillow, and when the current was reduced to its previous level, the patient settled back as before. This phenomenon could be demonstrated at will by an increase and a decrease in current.

In respect to the immediate process of awakening, each patient followed his customary pattern as with dextrose termination —some showing considerable crying and excitement, others not. All patients had an amnesia for the stimulation. Although four patients had previously had one or more convulsive seizures during hypoglycemic comas, they experienced none during the 15 trials of peripheral stimulation. The duration of peripheral stimulation necessary to awaken the comatose patients ranged from 10 to 33 minutes, with an average of 19.1 minutes. In 3 of the 15 awakenings intravenous dextrose was required, in addition to glucose by mouth, to attain a satisfactory convalescent state which would allow bathing, eating, etc. Four of the seven patients usually required this supplementary dextrose on other days, however. No formal comparison was made between the afternoon mental statuses of the patients following termination of their comas with peripheral stimulation and those following routine termination with dextrose alone. However, nursing reports from the personnel of the 2 to 10 p. m. shift, who knew little or nothing of the morning events, indicated that a noticeable improvement of mood was seen in those patients awakened with peripheral stimulation. Patients were more cheerful than usual, were more active, and in some instances unusually gay. On one occasion two of the female patients having their comas terminated with peripheral electrical stimulation spent most of the afternoon giggling in a silly, hilarious manner. This is in harmony with our observations as to the effect of peripheral electrical stimulation on a group of mentally ill patients receiving this form of stimulation as a therapeutic measure.

The results of 10 trials of peripheral stimulation in which blood sugar determinations were made are shown in Table 1. Peripheral stimulation resulted in a rise in blood glucose in 9 of the 10 trials, although the rise was negligible in 2 instances. In one arousal a decrease of 23 mg. per 100 cc. was seen.

Table 1 also shows that the duration of peripheral stimulation necessary to produce consciousness is not directly proportional to the duration of coma prior to stimulation or inversely proportional to the blood sugar level at that time. In the first trial of R. Z., 33 minutes of stimulation was required for her to awaken after a coma of 38 minutes, at which time her blood sugar was 31 mg. per

100 cc., whereas only 19 minutes of stimulation was required after 63 minutes of coma when the blood sugar was 23 mg. per 100 cc. In the case of B. B., 30 minutes of stimulation was required after coma of 88 minutes, at which time the blood sugar was 18 mg. per 100 cc., whereas 25 minutes of stimulation was required for a coma of 27 minutes when the blood sugar measured 60 mg. per 100 cc. In the first trial of L. N., 27 minutes of stimulation was required after 35 minutes of coma, at which time the blood sugar was 26 mg. per 100 cc., whereas only 20 minutes of stimulation was required after 75 minutes of coma, when the blood sugar was recorded as being at the extremely low level of 4.0 mg. per 100 cc. Although less peripheral stimulation was required to terminate the shorter comas of C. E. and D. S., it is noted that the blood sugar levels were essentially the same prior to both the early and the late terminations.

Table 2 shows the results of early and late terminations of hypoglycemic coma as related to the degree of rise in blood glucose. With each patient serving as his own control, this study shows that in four cases the arousals occurring after longer periods of deep coma were accompanied by a smaller increase in blood glucose than those occurring after short comas. In the fifth case there was an increase of 22 mg. per 100 cc. in blood glucose following stimulation after a coma of 88 minutes, but in the shorter coma, of 27 minutes, the level of blood glucose decreased from 60 mg. per 100 cc., when the stimulation began, to 37 mg. per 100 cc., when the patient had aroused.

TABLE 1.—*Blood Glucose in Patients Awakened from Hypoglycemic Coma with Peripheral Electrical Stimulation*

Name	Sex	Date	Rx No.	Units of Insulin	Time to Start of Deep Coma		Duration of Coma Prior to Stimulation, Min.	Duration of Stimulation, Min.	Blood Sugars, Mg/100 Cc.			
					Hr.	Min.			Pre-insulin	Start of Coma	Pre-stimulation	Immediate Post-stimulation
C. E.	M	8/12/54	45	150	3	45	50	20	138	12	26	28
		8/26/54	58	130	4	11	34	16	112	20	26	68
D. S.	M	8/12/54	87	200	3	25	50	25	109	18	20	26
		8/26/54	97	200	3	55	20	15	127	18	23	45
R. Z.	F	9/19/54	13	300	3	10	38	33	...	..	31	71
		8/26/54	18	225	4	02	63	19	105	26	23	40
L. N.	F	8/19/54	19	90	3	40	35	27	92	57	26	83
		8/26/54	24	80	3	25	75	20	...	18	4	45
B. B.	F	8/26/54	28	300	4	32	88	30	...	18	18	40
		9/ 9/54	36	175	3	45	27	25	120	12	60	37

COMMENT

Fifteen terminations of hypoglycemic coma in fifteen trials conclusively demonstrate the effectiveness of peripheral electrical stimulation in producing arousal from insulin-induced coma. As the awakenings produced so closely resemble those obtained when the same afferent stimulation is used to terminate barbiturate comas, a serious doubt arises as to the validity of the hypothesis of transcerebral stimulation of the diencephalon advanced by Hoffman and Wunsch and Riboli. It appears more probable that unidirectional currents of low amperage applied to the head of patients in hypoglycemic coma exert an analeptic effect through peripheral nervous pathways. We are inclined to speculate that experiments with animals in hypoglycemic coma paralleling those of Blachly and Brookhart with barbiturate coma would show that

TABLE 2.—*Increase in Blood Glucose Produced by Peripheral Stimulation as Related to Duration of Coma*

Name	Time in Deep Coma, Min.	Increase in Blood Glucose, Mg/100 Cc.	Time in Deep Coma, Min.	Increase in Blood Glucose, Mg/100 Cc.
C. E.	34	42	50	2
D. S.	20	22	50	6
R. Z.	38	40	63	17
L. N.	35	57	75	41
B. B.	27	—23	88	22

any analeptic effect of currents applied to the head would be abolished by section of the sensory nerves to that area.

Of particular significance are the two awakenings which occurred with no appreciable increase in blood glucose and the awakening which occurred with a decided decrease. These awakenings indicate that a return of consciousness is not dependent upon an increase in blood sugar, which was a concomitant phenomenon in the seven other instances.

From the data shown in Table 1, it appears that factors other than the length of insulin coma prior to stimulation or the level of blood sugar influence the duration of stimulation required to awaken comatose patients. One of these factors might be the amount of increase in oxygen brought about by hyperventilation occurring with peripheral stimulation. The determination of this factor, as well as the many others which influence the internal economy of cerebral neurons from the standpoint of anerobic metabolism or the utilization of aerobic metabolites, is obviously beyond the scope of the present investigation.

Hoffman and Wunsch report the occurrence of convulsive seizures in each of two patients in hypoglycemic coma who received cerebral stimulation at 10 ma. We exceeded this current in each of the 15 arousals with peripheral stimulation with trials of 30 seconds to a minute at the upper limit, 15-20 ma. The fact that seizures were not produced with peripheral stimulation suggests that cranially applied unidirectional currents might have some effect on the cerebral cortex, even though the analeptic action of such applications may be entirely due to peripheral stimulation.

The results of experimental studies which have been appearing over the past few years ‡ afford the basis for an explanation of the mechanism whereby peripheral electrical stimulation restores consciousness in patients with hypoglycemic coma. These studies stress the important influence of an ascending system of neurons in the cephalic portions of the brain stem on electrocortical and behavioral manifestations of alertness and the conscious state. Frequently referred to as the reticular activating system, it has been shown that this portion of the brain constitutes an extralemniscal sensory system which is essential to the maintenance of consciousness in animals and in man.§ It has also been shown that this portion of the brain is highly susceptible to depressant influences of a variety of agents, such as anesthetics, anoxia, etc., at levels which have no apparent influence on activity conducted over the classic lemniscal systems of the brain. It is highly probable that a similar depression of function occurs in this portion of the brain during hypoglycemic coma. Thus, it may be hypothesized that the multisynaptic internuncial organization of the reticular activating system is as vulnerable to diminished substrate for cellular activity as it is to interference by anesthetics. In hypoglycemic coma, therefore, the reticular activating system would not be sufficiently affected by normal afferent input that consciousness could be maintained. Extraordinary afferent input, such as that used in this study, in which continuing repeated nociceptive and proprioceptive impulses were administered, might activate this reticular system to the point that consciousness is restored.

Whether or not peripheral electrical stimulation as described above might succeed in a similar fashion in overcoming other types of comas of diverse etiologies remains an attractive speculation. We anticipate that it will. Likewise, it appears that peripheral electrical stimulation merits a therapeutic trial in those mental disorders characterized by states of impaired awareness.

SUMMARY AND CONCLUSIONS

Arousal from deep hypoglycemic coma was produced by peripheral electrical stimulation in each of 15 trials on seven patients.

No relationship was seen between the length of stimulation required for arousal and the duration of coma prior to stimulation or the blood glucose level.

‡ References 7 through 12.

§ References 13 and 14.

Two arousals occurred with no significant increase in blood glucose, and one arousal occurred with a marked decrease in blood glucose.

The demonstration of an analeptic action of peripheral electrical stimulation in hypoglycemic coma indicates that the same effect reported for similar currents applied to the head is most probably due to stimulation of peripheral nerves, and not to a transcerebral action.

Termination of hypoglycemic coma by means of peripheral electrical stimulation is not dependent upon an increase in blood glucose, but is thought to be due to an arousal mediated by the ascending portion of the reticular activating system.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Walter Wegner, M.D., President, Presiding
Regular Meeting, Nov. 18, 1954.

Auditomotor Mechanisms in Extratemporal Cortex. Dr. J. K. Merlis and Dr. C. Lombroso.

Detailed mapping of the cortical electrical responses evoked by acoustic stimulation in the cat reveals an area of consistent response in the anterior suprasylvian region. This area is topographically distinct from the three other auditory areas previously described, and acoustic potentials are evoked in it after ablation of the other responsive regions.

The suprasylvian area of each hemisphere is excited by the contralateral cochlea, whereas the ipsilateral cochlea appears to exert an inhibitory influence. The evoked potentials are insensitive to strychnine until this inhibitory influence is removed by destruction of the ipsilateral cochlea, whereupon they show a marked strychnine augmentation.

Observations of electrical stimulation of this region reveal that this is an area of low threshold for contralateral pinna movements, whereas stimulation of the primary auditory area in the ectosylvian gyrus evokes bilateral pinna movements. In addition to the contralateral pinna response, suprasylvian stimulation frequently evokes conjugate deviation of the eyes to the opposite side.

Synthesis of the data obtained with respect to the afferent and efferent mechanisms indicates that this suprasylvian area may be concerned with focusing attention to specific regions of the outside world, in contrast with the ectosylvian area, which is concerned with generalized alerting.

DISCUSSION

Dr. Walter Wegner: In the middle 1800's, there was a great deal of discussion about how the brain worked. The original investigators maintained that the brain worked as a whole. Beginning around 1860, investigators began to realize that different parts of the brain had a specialized function. After those investigations were confirmed and accepted, clinical localization of nervous disturbances could be made. It would seem that we are now going in the reverse direction, that we are getting various functions mixed together again in a given area, instead of being geographically isolated. Maybe functional localizations we talked about will have to be looked at again. I have found this paper very interesting, and a couple of questions occurred to me as Dr. Merlis gave it. One concerns the cytoarchitecture in these areas: Is there a close resemblance in the ectosylvian as compared with the suprasylvian area? Second, is Dr. Merlis acquainted with any human case material to which this work applies? We commonly believe that destruction of the auditory cortex in the temporal lobe on one side does not alter hearing significantly. Is there any case material in the literature which describes bilateral temporal lobe lesions? What happens to the hearing in these patients?

Dr. Warren McCulloch: There is a point which should be raised here, particularly with regard to bilateral lesions, not in the auditory cortex, but of the area anterior to it. Professor Galvardin, of Lyons, became interested in the same problem his father had worked on, i. e., auditory hallucinations which begin as arteriosclerosis in the later years of life. This is accompanied by overt movements in the muscles in the tongue, pharynx, and larynx. He selected one case for surgery. The man suffered from eternal chickens that informed him he was a good man, etc. They had become such a nuisance that he had himself incarcerated. Dr. Galvardin had removed one side of the face cortex, with transient relief. This cortex lies behind the lower end of the Rolandic fissure and down into the border of the Sylvian fissure. After the removal of the same cortex on the opposite side all movements in the pharynx and larynx ceased. He no longer heard the chickens, although they "meant" what they always had meant.

Dr. J. K. Merlis: I am not an expert in architectonics, but I can cite Rose's data which indicate that there is a change in crossing the sulcus. The ectosylvian gyrus is dis-

tinctly different in its cellular structure from the suprasylvian groups. As for the influence of temporal lobes lesions on hearing in man, in the experimental primate, the monkey, removal of the superior temporal gyrus, and of the posterior insula bilaterally, does not abolish appreciation of sound. It seems to be reasonable that this might also be true in man.

Visuomotor Function in the Cerebral Cortex. Dr. D. Denny-Brown and Dr. R. A. Chambers.

Disturbances of visual perception (agnosia) result from damage to parastriate areas of the occipital cortex, in which areas concerned in visuospatial aspects of perception and of object recognition by vision have been postulated. Studies of monkeys after complete removal of Area 17 by suction, leaving Areas 18 and 19 intact, showed that prehensile reactions could be stimulated by moving objects, and that placing reactions to surfaces and edges could still be elicited. Optic righting in space was also intact. Bright illumination inhibited these reactions. Visuomimetic behavior and visual recognition of still objects were absent. The lateral geniculate bodies were completely degenerated. Removal of Areas 18 and 19, leaving Area 17 intact, impaired spatial judgment and led to confusion by moving objects, though placing and prehensile reactions remained intact. The posterolateral nuclei of the pulvinar were degenerated.

Removal of the lower part of Areas 18 and 19 and the temporal lobes, as well as Area 17, left visual prehensile and placing reactions, and optic righting, intact and abolished fear from visual stimuli. Linear visual contrast was the adequate stimulus for spatial and prehensile responses. Removal of the upper parts of Areas 18 and 19 and the parietal lobes, as well as Area 17, abolished visual prehension, placing, and righting but left strong fear and flight reactions, especially to brightly illuminated surfaces. Dark contours then offered attraction.

These experiments indicate that there is a double visuomotor mechanism in the cerebral cortex, one relating to the detailed perception of still objects, the other to moving objects. In each there is a horizontal organization into an upper segment, which, with the posterior parietal lobe, is related to spatial reactions, and a lower segment, relating to tropisms to objects. Each is independent of the other. The lower segments of Areas 18 and 19 and the temporal lobe serve a powerful negative (avoiding) response to illuminated objects. There was no evidence of a separate area for spatial or object recognition, though the mechanism is such that separate disorders of these can be produced by small bilateral lesions.

DISCUSSION

Dr. Paul B. Jossmann: Observations on humans with visual agnosia confirm Dr. Denny-Brown's experimental work. Recognition and identification are facilitated when objects are in motion. Experiments undertaken with normal subjects show that on exposure of cinematographic films moving objects are recognized better than nonmoving objects. I should like to ask whether the experiments have indicated a specific relation of gnostic functions to Areas 18 and 19 of Brodmann.

Dr. Robert Schwab: Does Dr. Denny-Brown have any idea which system is involved in stereovision, which these monkeys evidently have?

Dr. Walter Wegner: The lesions Dr. Denny-Brown has demonstrated in these monkeys were bilateral. He has also been interested in the visual phenomena resulting from lesions in these areas in human beings, and many such lesions are unilateral. I wonder if he would comment on his observations regarding the visual phenomena in unilateral lesions in such patients. Some years ago Dr. Dandy, I believe, reported a case in which he approached a third ventricle tumor through the posterior part of the corpus callosum and noted afterward that his patient was unable to recognize objects which appeared in the left visual field. If a friend approached from the left side, he would not recognize him but would recognize him readily when he got into the right field of vision. The surgeon presumed that this defect was due to cutting some fibers in the corpus callosum. It might equally well have been due to damage by retraction or contusion of the right hemisphere. In any event, it would suggest an interpretive function in the right hemisphere, which we ordinarily believe resides in the left hemisphere.

Dr. D. Denny-Brown: To take Dr. Wegner's question first: I am sure these disturbances can be shown by unilateral lesions, but they are difficult to test in a monkey because he does not keep his eyes fixed. We have in the ward at present a patient with complete hemianopsia

for object recognition, as a result of occipital meningioma, but who can pick up movement in any part of the affected field of a quite small object. She could not tell you whether it was square or round, but only that there was something moving. It is difficult to get exact anatomical evidence. I would suspect Area 17 had been damaged on one side in Dandy's patient.

As to difficulty in identifying persons: Most writers do not make movement an important factor. But in Dr. Jossmann's patient and in one described by Holmes, and in others I have seen but not studied in detail, movement is obviously very important. I would think that one trouble in investigating agnosia is in knowing where to begin. It is like being presented with a mass of details and trying to sort them out. The criteria chosen for current classifications may not be of importance in the nervous mechanism. The present work aims to define the most elementary physiological factors in visual recognition and relate them to specific parts of the mechanism. The finding of two distinct cortical mechanisms, one related to the genic-ulostriate projection, the other to the pulvinar-parastriate projection, gives a new approach.

I do not know about stereovision in monkeys. It is difficult to judge depth perception in an animal. Some clear-cut clinical cases would be necessary to decide that question. At present we do not even know why it is that the object has to move to be seen. Movement of the head, so as to produce apparent movement of the object, is not effective.

Walter Wegner, M.D., *President, Presiding*
Regular Meeting, Dec. 16, 1954

Malformations of the Nervous System. DR. PAUL I. YAKOVLEV.

A series of specimens showing circumscribed defects in the cerebral mantle were shown and the evidence was presented that these defects in structure of the brain are laid down not later than the end of the second month of gestation. The common characteristic of these defects is their tendency to occur in the zones of the primary fissures (Sylvian, Rolandic, medial orbital), especially in the midline in the zone of the telencephalon medium and the roof plate of the prosencephalon.

The available material illustrates all degrees of transition—a gradient of severity—of the malformation of the hemisphere from a simple agenesis of the corpus callosum, consisting of failure of the commissural fibers to cross the midline but without any other abnormality in the structure of the cerebral hemisphere, to a more or less extensive symmetrical defect in the development of the cortical plate, amounting in some instances to a complete agenesis of the cerebral mantle.

There exists a tendency to confuse the two distinct issues; namely, the issues of the causal and of the formal origins of malformations, and to search for a unique causal mechanism for all such defects. The so-called "vascular theory," claiming the failure of development of blood vessels supplying various parts of the cerebral mantle to be the cause, is most appealing to many. Yet a careful study of the morphology and architecture of the forebrain in these malformations permits one to assert that blood vessels fail to develop because of the primary failure of organogenesis of the brain.

Whatever may be the causal origin of these defects, the key to the formal origin of these malformations is most likely to be found in the interference with the normal processes of organogenic induction, upon which depends the regional differentiation of the brain.

DISCUSSION

DR. WALTER WEGNER: It is easy to see how Dr. Yakovlev's study of neuroanatomy has led to an interest in the study of malformations. Dr. Yakovlev has told us that these malformations depend upon influences which occur early in the life of the fetus. No doubt there are other malformations, or other deformities which occur later, due to noxious influences. I have wondered about the vulnerability of the brain at different periods. Is it more vulnerable in the early periods than later? Is there evidence that if the fetus is exposed to radiation during the first few weeks of gestation, it is more vulnerable than later on? Or if the mother contracts measles, is the fetus more vulnerable at one period than another?

DR. WILLIAM H. SWEET: If I understand Dr. Samuel Hicks correctly, he states that different noxae at the same stage of embryonic development tend to produce different types of malformation or defect. On the contrary, the same type of malformation may be produced

at different stages in embryonic development by appropriate variation and dose of the deleterious agent. (I am referring to his paper "Injury of the Central Nervous System Incurred During Fetal Life," presented at the December, 1954, meeting of the Association for Research in Nervous and Mental Diseases.) Is there any difference between his point of view and yours, Dr. Yakovlev?

DR. CLEMENS BENDA: Dr. Yakovlev's masterful contribution is a great stimulus to anyone engaged in this field. I would like to say a few words about the practical importance of those congenital malformations. Many physicians think that this is a rather limited field of special interest. Studies on our autopsy material of now more that 300 cases indicate that about 30% of children and adults suffering from severe mental defects have some type of developmental disorder of the prenatal period. Some of them are of a genetic, some of an accidental, nature, and it is extremely important for the physician to arrive at a correct clinical diagnosis because so many other problems are involved, like the question of more children, genetic factors, reasons for the anomalies, and possible prevention.

DR. D. DENNY-BROWN: As I understood Dr. Yakovlev's thesis, the primitive cerebral vesicle can develop into the corresponding regions of brain, except for one symmetrical segment. This defective segment may remain as a thin-walled cyst, either without any recognizable neural structure in its wall or with a layer of poorly differentiated cerebral tissue. Such a process would imply the action of some restricted agent on the anlage of cerebral tissue of the affected region of the cerebral vesicle at a very early stage, different from the diffuse effect of radiation, and sharply restricted in area. Did Dr. Yakovlev find any remnants in the cyst wall to give any suggestion of the nature of the noxious agent? Is there always a cyst wall representing the original cerebral mantle? The failure of development of corpus callosum suggests that the remnants of the vesicle were not such as to serve as a medium for the growth of nerve fibers Do any of the aberrant fibers that entered the fornix system follow it down to the hypothalamus and cross there?

DR. BERTRAM SELVERSTONE: I was interested in the hydrodynamic changes which result in a wide-open communication between the ventricle system and the subarachnoid space. Would Dr. Yakovlev say a few more words about that?

DR. PAUL I. YAGOVLEV: In regard to Dr. Wegner's question, I would say that there is definitely a great difference in vulnerability of the brain, depending on the stage of its development. Generally it seems that embryos of up to 3 months are better protected against hazards such as asphyxia, the ultimate cause of damage to all living tissues, especially the brain, than are fetuses in later stages of gestation. Second, the effect of any noxious factor will differ according to whether the factor comes into play before or after completion of the organogenesis of the neuraxis, which is about the end of the third month. The factors operating during the first two months will generally tend to cause greater deviations from normal in the ultimate form and structure of the neuraxis than those that come into play later during the fetal period.

In regard to Dr. Sweet's question: The radiation effect on living tissues not only interferes with the morphokinetic processes of the organogenesis of the developing brain, but also, and unavoidably, kills the tissues producing severe destructive lesions. Dr. Hicks's work throws much light on the causal origin of malformations resulting from the effects of radiation. As yet they do not permit one to learn much about the formal origin of the monstrosities of configuration and structure of the nervous system. There are, then, two distinct problems in the embryonal and early fetal pathology: One problem is what does the damage—the causal origin. The other problem is at what time of development the malformation arises and with what consequences to subsequent development of structure and function of the brain. This is the problem of formal origin of these peculiar brains which I have shown you tonight. The material coming from the autopsy rooms usually affords very few, if any, data to answer the question of what caused the abnormalities. On the other hand, a careful anatomical study of these specimens in serial sections, which is *sine qua non* in this matter, permits one to recognize in the departures from the normal the basic principles which govern the structuring and organization of the brain as an organ—they reveal the formal origin of these defects. The nature of the material with which I deal is not suitable to answer the question of causality in the narrow sense of the etiology of these malformations. Only experiments, such as, for example, those of Dr. Hicks, will, with further improvement in the methods used, permit

insight into etiologic factors which cause these malformations. There is no contradiction between these two methods, i. e., the inductive experimental and the analytical morphological —they are mutually complementary; both are necessary.

Dr. Denny-Brown brought up an important issue. Indeed, the isolated ectopic islands of differentiated cerebral substances containing nerve cells, glia, and myelinated fiber bundles in the subarachnoid spaces of the pia-ependymal membrane roofing the defect in the cerebral mantle are extremely common. It is impossible to assume that by some mischance they have been split off from the brain itself and pushed into the subarachnoid space to continue their elaborate histogenesis almost undisturbed. It is much more likely that these islands of cerebral substance in subarachnoid space have developed there in situ with the primitive meninges from the elements of the ectoblast before these elements became irrevocably committed to develop into the nerve cells, glia, or soft meningeal envelopes. To my way of thinking, these and other similar findings in the schizencephalic malformations of the end-brain bespeak a disorder of the regional induction processes occurring as early, perhaps, as the presomite or early somite stage, i. e., in the second or third week of gestation.

Dr. Selverstone asked about the nature of hydrocephalus in these malformations. The hydrocephalus is clearly not the cause, but the function, of the arrested development of the cerebral wall. If the defect is limited to a small area of the brain wall while the surrounding parts continue to develop normally, there is usually no hydrocephalus. If, on the other hand, the area of arrested development of the cerebral mantle is extensive and, especially, if the defect occurs near or in the roof plate, the thin vesicular brain wall yields passively and adapts to normal pressure of the fluid contained within the ventricle, and so the hydrocephalus ex loco minoris resistentiae results. In the case of these cleft-forming defects in the cerebral mantle there is no evidence, or a need to explain the hydrocephalic enlargement of the usually single ventricular cavity of these brains on the basis of obstruction of cerebrospinal fluid circulation or disturbance of its production and absorption.

Response of the Central Nervous System to Focused Ultrasound: Experimental Results. Dr. Walter C. Cotter, Dr. Walle J. H. Nauta, Dr. Theodor F. Hueter, and Dr. Thomas Ballantine Jr.

An ultrasonic generator was constructed with two aims in mind: (1) production of focused ultrasound, and (2) great flexibility in the parameters that determine dosage. By means of a lens, ultrasound has been focused into a region measuring 0.9×9 mm. at 2.5 mc. and 2.5×35 mm. at 1 mc. The focal intensity can be varied from 100 to 2000 watts per square centimeter. The production of pulsed ultrasound with variable pulse period is possible.

That small lesions could be produced with this apparatus was demonstrated when mice were rendered monoplegic by irradiation of one-half the spinal cord. Production of lesions in stereotactically predetermined sites in cat brain showed the accuracy with which a region of focal damage could be predicted.

Investigations into the parameters determining dosage have been started, using as an end-point weakness of one or both hindlegs of mice irradiated over the 10th thoracic vertebra. We have used pulsed ultrasound at a constant duty cycle of 0.4 sec. pulse width and 1.0 sec. pulse period, but have varied the number of pulses and the intensity of ultrasound. A statistical analysis of data on over 800 mice, irradiated with ultrasound at 1 and 2.5 mcps., has established a relationship between dosage and biological effect which indicates there is a threshold of ultrasound amplitude below which no damage occurs, and that above this threshold damage depends more strongly on the amplitude of the ultrasound used than on the duration of exposure.

Using these relationships, we are presently engaged in producing lesions graded as to size and shape in cat brain. It has been possible, for example, to destroy selectively the ventral anterior nucleus of the thalamus by a proper dose of focused ultrasound. It is hoped that these investigations will reveal the degree of accuracy with which a cerebral lesion of a specific size and a specific shape can be produced in a specific location without undesired side-effects. Only with such knowledge will it be possible to decide whether this tool is ready to be taken out of the research laboratory and put into clinical use in neurologic surgery.

DISCUSSION

Dr. Thomas Jones: What are the possibilities for further localizing the lesion by having multiple focus or crystal and lens with radiation at a 90 degree angle?

DR. JAMES C. WHITE: Do the authors envisage this method as a possible means of destroying tumor tissue? If ultrasound can be focused accurately enough, it might be a way of dealing with areas where a surgeon cannot use a knife. It will take a great deal of future work to focus the area of transection. It will have a great potential use for leucotomy for psychiatric patients and patients with pain. It will have to compete with lesions being made by the introduction of radioactive isotopes, or with radio frequency currents, which can be placed so very accurately. You have seen the work of Lindström in destruction of Areas 9 and 10 in ultrasonic lobotomy. I have admired the speakers for wanting to learn all about the effects of ultrasound on animal tissues in the laboratory before trying to take it into the clinic. I think Lindström has gone at it the other way around.

DR. WALTER WEGNER: About this means of destroying tumors, would the authors tell us about the acute reaction of tissues? Is there severe swelling? Would one have to consider that in using it for tumors?

DR. RAYMOND D. ADAMS: I examined two or three of these sections, and there are several unusual features. Everyone wants to know what ultrasound does to the elements within the nerve tissue, as well as how accurately this agent can be focused on the nervous system. In the sections I saw with a fairly intensive radiation, there is destruction of nearly every tissue element: cell, myelin, astrocytes, microcytes, and even blood vessels are completely destroyed. There is almost no hemorrhage in the lesion, suggesting that these vessels must be sealed off almost at once by that which damages the tissue. It will be of interest to the neuropathologist to see if grading doses of this radiation will wipe out parts of the tissues more than others.

DR. HARRY C. SOLOMON: What are long-term effects of ultrasonic irradiation, say three, six, or nine months later? Will it be a continuous picture of destruction? Is it possible to give a dosage that is sufficient to concuss or knock out the activities and then have recovery take place in the course of days thereafter?

DR. H. THOMAS BALLANTINE JR.: I would like to express my appreciation of the discussion and the questions raised regarding this relatively new technique. As to techniques of multiple focusing, there is a feasible method which is used by Fry and the University of Illinois. It produces a more punctate lesion, but the multiple-focusing method is more difficult in application. We are not convinced that it is necessary to use a multiple-beam technique to get a small area of destruction.

As to the ultrasonic treatment of brain tumors: There has not been any evidence that abnormal cells are more sensitive to ultrasound than normal. However, all cells can be destroyed within a certain region. If such destruction would allow for shrinkage of tumor without damage to vital areas of normal brain, some symptoms might be alleviated.

As to edema: This factor must be discussed in terms of dosage and the way in which the ultrasound is applied. If the method of application is such as to produce gross heating of tissue, a great deal of edema will result. If the tissue is "concussed," it is unlikely that as much edema will result as though the tissue were burned. Dr. Adams has put his finger on the crucial point—dosage. We do know that both heat and concussive effects are present, and it is most difficult to separate these two effects and to analyze them.

In answer to Dr. Solomons question as to the long-term effects of ultrasonic irradiation, there is no reason to believe that there is continuing damage following ultrasound, as there is in x-ray treatment. Whether brain tissue can be "concussed" in such fashion as to give a temporary syndrome that can be evaluated we do not know. There are reports that central nervous system function has been interrupted for a period of time, following which recovery has taken place. This we have not seen, however.

CHICAGO NEUROLOGICAL SOCIETY

Benjamin Boshes, M.D., *President*
Oscar Sugar, M.D., *Secretary*
Regular Meeting, Jan. 11, 1955

Spontaneous Intraspinal Hemorrhage and Paraplegia Complicating Bishydroxycoumarin (Dicumarol) Therapy. DR. E. T. YUHL (by invitation).

Paraplegia complicating anticoagulant therapy with bishydroxycoumarin is extremely uncommon. One instance has previously been reported by Arieff and Pyzik, but the patient did not

undergo operation. The present report describes spontaneous epidural, subdural, and subarachnoid hemorrhage consequent to bishydroxycoumarin treatment and verified by laminectomy.

A 66-year-old white man was maintained on ambulant bishydroxycoumarin therapy because of a posterior myocardial infarction. Four weeks after onset of treatment the patient noted increasing back and neck pain, with onset of radicular pain in both lower extremities, associated with weakness in the legs, at which time he was hospitalized. The day after hospitalization the weakness progressed to nearly complete paraplegia and was associated with the sensory level at T 11. The prothrombin time was 11% of normal.

A single blood transfusion and 100 units of vitamin K_1 oxide were administered intravenously prior to laminectomy. At operation a large epidural hematoma at T 12 and L 1, a larger subdural hematoma, and diffuse subarachnoid hemorrhage were identified. The hematomata were removed.

There was rapid recovery of motor function for 48 hours, with subsequent slow improvement in motor function and all modalities of sensation. At the time of discharge the patient was able to walk with assistance, but bladder control did not return.

DISCUSSION

DR. R. B. RICHTER: Dr. Yuhl's case report is a timely one in an era when newly developed therapeutic agents and techniques occasionally, and often unexpectedly, are themselves the cause of serious complications. Nowadays one must be constantly on the qui vive for such iatrogenic complications, because when they are unusual, as they were in Dr. Yuhl's patient, their true nature can easily escape detection. If the present patient, for example, had been admitted to a strange hospital where the history of bishydroxycoumarin therapy was not known, a diagnosis of dissecting aneurysm of the descending aorta with paraplegia might easily have been made and all chance of saving the cord forever lost.

There is one point in the management of this and similar cases that I should like to consider. It has become customary to depend, or even to insist, upon myelography for the localization of the level of spinal cord compression. This is all well and good, considering the well-known errors to which sensory levels may occasionally lead, especially in cases of acute pressure. On the other hand, it is a maxim that in the surgical treatment of acute or rapidly progressive spinal cord compression time is of the essence. It is not always possible to carry out myelography immediately on a truly emergency basis. When the disadvantages of some inaccuracy of localization are balanced against the more serious ones of loss of time, where two or three hours may well determine the outcome of the decompression, would it not be better to carry out immediate laminectomy guided by the sensory level? It should not be forgotten that usually a meticulous and expert neurological examination will afford data adequate for practical purposes in placing a laminectomy.

DR. ALEX ARIEFF: This report differs from ours in that the bleeding was proved by operation. In the case we presented, we inferred the hemorrhage was intramedullary, for when the spinal was done there was no bleeding. Neither was there evidence of subarachnoidal blocking. All clinicians should be interested in this report. One cannot prove the symptoms due to bishydroxycoumarin therapy even in a sensitive person. However, in two cases now reported, hemorrhages have occurred both in and about the spinal cord as a result of bishydroxycoumarin therapy, so that it behooves us to pay attention to these patients while they are receiving medication of this type.

DR. ROBERT F. HEIMBURGER, Indianapolis: I suggest that these lesions not be operated upon without a myelogram. I have never seen a case of paraplegia from bishydroxycoumarin, but I have seen a number in which it was rapidly progressive from an epidural abscess. I have seen the sensory level rise precipitously in a period of two or three hours, and for that reason it is probably necessary to obtain a myelogram in order to get localization. The rapid rise in sensory level indicates that the spinal cord lesion is incomplete when the patient is first seen and gradually becomes complete with increasing pressure. If the neurosurgeon waits until the sensory level remains stationary for several hours, he misses his optimum chance to save the function in his patient's legs. If he operates early, when the level is low, he may well expose an area of normal spinal cord and miss the more cephalad lesion. If myelography is done as soon as a motor and sensory deficit is established, the chances of localizing the lesion and sparing function are more assured.

DR. BENJAMIN ROSHES: I might comment not on paraplegia following bishydroxycoumarin administration, but on an instance of embolization from a pelvic source in which bishydroxycoumarin had been given, with a rapid drop in the prothrombin time. Meningeal signs appeared

very rapidly from cerebral bleeding. In another case, following coronary thrombosis with bishydroxycoumarin therapy, a posterior inferior cerebellar artery syndrome developed, which cleared up when the bishydroxycoumarin was stopped. In still another instance a patient had developed a deep involutional melancholia, with considerable guilt. Because of a religious conflict, she could not use a gun, poison, etc., and, therefore, took bishydroxcoumarin over a period of months. Her red blood cell count was well under 1,000,000, and the prothrombin time was down to 12% at the time the trouble was discovered. When the drug was stopped, the blood picture returned to normal. Preliminary transfusions were needed.

DR. E. T. YUHL: Dr. Heimburger, in answer to your question with regard to myelograms, this man did have a myelogram. The procedure took approximately one hour or so. After that time the level had risen, and a clear-cut sensory level was obtained for the first time. It was unfortunate that we could not do a satisfactory lumbar puncture, for there was hemorrhage in the subarachnoid space.

The neurosurgeon whose patient this was considered laminectomy without a myelogram. However, the resident suggested the procedure because the exact level of the lesion was in doubt. I wish to thank you and Dr. Richter for your discussion.

Neonatal and Prenatal Enamel Hypoplasia in Children with Cerebral Palsy. DR. MAURY MASSLER (by invitation) and DR. MEYER A. PERLSTEIN.

The growing and calcifying enamel records within its structure even minor variations in metabolism, particularly calcium metabolism, in a manner similar to the rings formed in trees. Daily and seasonal variations are recorded within the microscopic structure of the enamel. The neonatal ring forms a very convenient line of reference for dating prenatal and postnatal effects on the enamel and dentin when these are examined histologically (tooth ring analysis). Major disturbances can be seen clinically as enamel hypoplasias. The chronology of such hypoplastic defects can be determined with accuracy within one or two months during the first year of life and to within six months thereafter.

Two hundred children with cerebral palsy were examined for dental defects and dental dysplasias. It was found that neonatal (and prenatal) enamel hypoplasias occurred in 30% of these children, in contrast to an incidence of 0.7% in a large group of normal children. A subdivision of the children with cerebral palsy due to kernicterus revealed the fact that approximately 80% showed neonatal or prenatal enamel hypoplasias. Twenty per cent were in the prenatal area. Intrinsic green staining of the enamel was also seen in a few cases. Since prenatal hypoplasia (especially green enamel) is virtually unknown in normal children, this occurrence is sufficiently high to merit further investigation as to possible prenatal factors in the etiology of kernicterus.

Histologic examination of the teeth of children with kernicterus should permit more exact dating of the time of injury in these children.

The incidence of neonatal hypoplasia in the children with cerebral palsy associated with birth injuries due to anoxia, breech, dystocia, etc.—athetoids or spastics—was 17%. This incidence is much less than occurs in the group with kernicterus, but much higher than in normal children. Prenatal hypoplasia was not observed in this group.

The incidence of other dental disorders, such as dental caries, gingivitis, and malocclusions, were not markedly different in the cerebral palsy group than in normal children. However, bruxism was a frequent occurrence (82%) in children with cerebral palsy.

DISCUSSION

DR. R. P. MACKAY: I should like to ask Dr. Massler whether he can give us any hint about the intrauterine events at five months which might lead to this alteration in enamel formation?

How can you injure the fetus except through the mother?

DR. MAURY MASSLER: I suspect that the effect would be directly on the fetus rather than through the mother.

DR. BENJAMIN BOSHES: Did this defect show up in any cases of proved cerebral agenesis, where the brain has failed to develop? Usually it is seen in kernicterus, and I wonder how the two are connected.

DR. R. P. MACKAY: What about the time of eruption of the deciduous teeth? Does the tooth reflect the variations in time, from the premature beginnings in the anlagen of the tooth structure, or what factor might delay the development of the tooth-bearing tissue?

DR. MAURY MASSLER: There is no relationship between the eruption of the teeth and the deposition or the beginning of the formation of dentin. In cerebral palsy children the eruption is delayed. There is no relationship between the enamel defect and the time of eruption of the teeth.

Paroxysmal Anterior Cerebral Bradyrhythmia. DR. J. S. GARVIN, MRS. E. L. GIBBS, and DR. F. A. GIBBS.

A study was made of 133 patients whose electroencephalograms showed paroxysmal slowing in the frontoparietal area with shifting slowing in the temporal areas, and clinical correlates were determined.

Although the electroencephalographic pattern is precise and ordinarily increases during drowsiness, while diminishing during sleep, no specific etiologic factor was determined. Over 75% of such EEG's, were of unknown etiology, and only 4 patients, or less than 4%, had brain tumors. Eight patients had arteriosclerotic hypertensive vascular disease, a small proportion for this age group, and when patients with a clinical diagnosis of arteriosclerosis are studied with electroencephalograms, we do not find this pattern.

This pattern occurs almost twice as frequently in women as in men, making it the only electroencephalographic abnormality except for petit mal in which the sex incidence is significant.

The clinical history usually consists of a sudden onset of convulsions during the period between 30 and 55 years of age. Seventy-four per cent of the patients had convulsions. Eighty per cent had no objective neurologic signs, and those that did, except for the brain tumor patients and one patient with an old cerebrovascular accident, had minor signs. Headache, dizziness, memory loss, and mental deterioration were the commonest symptoms.

Twenty-six of these patients have had more than one electroencephalogram. The pattern may develop from a slow-wave focus in the temporal area and show gradual progression, as occurred in one of the brain tumor cases. The pattern may be present at the time of the first examination and may disappear with the patients becoming symptom-free. Several of the patients have followed this course, and one has begun to show the abnormality again. The final evaluation must wait for repeat electroencephalograms on a larger number; however, we feel at present that this is a well-defined electroencephalographic pattern, and that in the absence of localizing neurologic signs further investigative procedures need not be carried out.

DISCUSSION

DR. R. P. MACKAY: I, too, am interested in the relationship between this abnormality and sleep. Inasmuch as we know that slowing of the EEG is one of the characteristic signs of sleep, and the authors stated that these abnormalities were apt to disappear during sleep, how could one in any case see the paroxysmal slowing during the constant slowing of sleep. If slowing of the EEG is characteristic of sleep, may we perhaps assume that these patients are suffering from a transient period of subclinical sleep, if we might use such a term, without there being full somnolence?

DR. ALEX ARIEFF: When the electroencephalogram shows a diffuse abnormality at least in the anterocerebral part of the brain, it indicates something wrong on a laboratory basis that is helpful in the clinical diagnosis. However, I do not know that we can deduct that this is going to be of a specific clinical entity.

DR. BENJAMIN BOSHES: I should like to interpose a brief discussion. As I watch these presentations, particularly such a laboratory phenomenon, I always wonder what is going on as far as the patient is concerned. I think it is rather important to ask oneself that question, because the findings are all tempered by the way in which the relationship affects the clinical picture. I wish to call attention to the fact that we neurologists are the last to be consulted.

Two cases are presented; both patients had paroxysmal bradyrhythmia, and both were women in the late 40's with proved sphenoidal meningioma. One of them suffered from abdominal pain. I studied her briefly. She entered one of the University Hospitals nine times in one year and was given a clean bill of health. They called it paroxysmal abdominal distress, as well as paroxysmal bradyrhythmia. I asked to have her brought in at the time of the pain, and she had a typical picture of abdominal distention. We operated on her the same afternoon and found three stones in the cystic duct that were causing her pain.

Unusual Myopathy: Presentation of Two Cases with Muscle Biopsies. Dr. R. B. Richter and Dr. E. M. Humphreys.

Two patients afflicted with disease of the muscles who on physical examination appeared to be much alike were presented. Both were young women in whom the clinical picture bore more than a superficial resemblance to muscular dystrophy except that in neither was the condition progressive. In both there was weakness, greatest in movements at the shoulder and hip joints, with well-marked atrophy of shoulder girdle muscles, but little or none of the hips and legs. The tendon reflexes in the arms and legs were diminished but still present in the two cases. Neither patient was seriously incapacitated, but both had a great deal of difficulty in climbing stairs, rising from the ground, and reaching for objects above the head, and both assumed the erect from the supine position in the manner typical of patients with muscular dystrophy.

Despite these similarities, there were fundamental differences between the two patients, and it was clear that they suffered from quite different and rather unusual diseases. In the first patient the onset of the weakness had followed a febrile illness four years before, had progressed during the following two years, and subsequently had remained unchanged. A muscle biopsy revealed, in addition to atrophy, hyaline and other degenerative changes of the muscle fibers, an inflammatory reaction unlike that usually seen in the rheumatoid diseases in that the exudates of large and small lymphocytic cells occurred in compact aggregates or nodules unrelated to blood vessels. In the second case the symptoms were apparent in early infancy; she was an inert baby, who was very slow to support her head and body and to walk and who was thought to be double-jointed because she was so limber. Throughout childhood she became easily fatigued, fell frequently, and was generally clumsy. After puberty her strength appeared to improve and had remained unchanged in early adult life. There was now appreciable, but not excessive, hypotonia of the extremities, and, unlike the first patient, she had a somewhat myopathic facies. Muscle biopsy revealed only focal areas of degeneration of muscle fibers with hyaline change and increase of nuclei between the fibers and within the sarcoplasm. The most striking part of the muscle abnormality was in the collection of not highly abnormal fibers into small, irregularly shaped bundles separated by loose fibroareolar tissue, which included few fat cells.

The condition in the first patient was thought to be a chronic myositis for which no specific etiology could be established. The second case was regarded as an example of that comparatively rare form of amyotonia congenita in which the disorder is to be attributed to congenital myopathy rather than to the spinal gray matter.

DISCUSSION

Dr. Herman Chor: First, were creatine-creatinine studies done? Second, were electromyographic studies done? Creatine-creatinine studies should help us in making a diagnosis in the dystrophies.

In the second case, I certainly agree with Dr. Richter that the early history suggested Oppenheim's disease. In this muscle disorder we have two types. There is a malignant type in which the patient usually dies early of intercurrent infection; and there is the more benign type, in which the child may survive but never develops normal muscular strength. A few of these children go on to adult life. I should also like to ask whether chemical studies were done in the second case.

Dr. R. B. Richter: Creatine and creatinine determinations were made on two 24-hour urine specimens of each patient. Both women were small-boned and had correspondingly small muscles generally, so that, as would be expected, the creatine excretion in neither was very high. Nevertheless, it appeared to be greater than would be expected in the second patient, the one with congenital myopathy. I am unable to agree with Dr. Chor, however, that such information is of any decisive value in differentiating one kind of muscle wasting from another, in particular, the myopathic from the myelopathic. At least, it has been my experience that increased creatine excretion is seen as frequently, and in the same quantitative ranges, in amyotrophic lateral sclerosis as in muscular dystrophy.

I also find myself at variance with Dr. Chor's proposition that amyotonia congenita is a single disease of which there are two clinical varieties—the progressive, lethal form of Werdnig-Hoffmann and the benign form of Oppenheim. It is true that we have examined the nervous systems of a good many cases of amyotonia congenita in our laboratory, patients dying sooner or later in infancy or early childhood. In these we invariably found, as did Grinker and others, that there was extensive disease of the motor neurons of the anterior gray matter. Dr. Lichtenstein, I suppose, has had the same experience, and it is this which inclines him to the view that the disease in our second patient was also primarily spinal. It is not, of course, possible to

exclude this possibility short of a pathological examination of the cord, but I do not believe so. To me, what makes our second case of real interest is the fact that it corresponds so closely clinically with the four familial cases of congenital myopathy reported by J. W. A. Turner. His patients presented classic features of amyotonia in infancy, and as they grew into early adult life, they lost the myotonia and presented instead the muscle wasting and weakness of a myopathy. The muscles and the nervous system of one of Turner's cases were examined with great care and thoroughness by Greenfield, who found no alterations in the spinal gray matter, and observed changes in the muscles in general like those described by Dr. Humphreys, in our second case. It is also impressive to me that so astute and rigorous an observer as Spiller reported a clinically valid case of amyotonia congenita in which he found no changes whatever in the spinal cord. It would seem that our second case furnishes strong presumptive evidence for the view expressed by both Turner and Spiller that amyotonia congenita is a symptom complex which at times is the result of spinal muscular atrophy of the Werdnig-Hoffmann type, but which on occasion may be the consequence of congenital myopathy.

As to Dr. Boshes' question about a unilateral crossed adductor reflex, I can only say that I believe this is an artifact in the film. In repeated examinations, contraction of the adductor muscles on testing for the patellar reflex was inconstant, and was present with equal frequency on the two sides, and there were no other indications of corticospinal tract involvement.

Benjamin Boshes, M.D., *President*

Oscar Sugar, M.D., *Secretary*

Regular Meeting, Feb. 8, 1955

Clinicopathologic Report of an Acute Familial Encephalopathy in the Newborn Infant. DR. CHARLES BARLOW (by invitation).

Two of three children of a healthy mother and father developed a central nervous system illness characterized by repeated convulsions and fasciculations of the face, ultimately leading to death. The pregnancy and delivery were uneventful, and the infants were apparently healthy for the first eight hours of life. They both died between 30 and 36 hours of age.

Microscopic examination of the nervous system revealed widespread acute regressive neuronal alteration with fatty vacuole formation in neuronal cytoplasm. There were generalized vascular engorgement and early regressive change in astrocytes and myelin. The clinicopathologic circumstances seem best interpreted as a toxic or metabolic accident. It is regarded as significant that the mother was able to provide adequately for these infants in utero, possibly by supplying a substance the infants could not manufacture, or by performing a detoxifying function the infants themselves could not accomplish.

DISCUSSION

DR. R. B. RICHTER: It would be generally agreed by most neuropathologists, I believe, that very wide areas in the field of degenerative diseases of the brain of the infant, and perhaps even more so in the case of the newborn, remains terra incognita. Although Dr. Barlow's description of these two cases provides no clues as to etiology, it is, nevertheless, of considerable interest. It is clear that these cases are not instances of the ordinary "toxic encephalopathy" of infants. As Dr. Barlow points out, no such acute fatty degeneration of neurons has been recorded in any of the rather numerous and extensive studies of fat in the brains of newborn and very young infants. This feature, together with the familial incidence, makes the material seemingly unique and quite worthy of the documentation that Dr. Barlow has given it.

DR. BENJAMIN BOSHES: Were there any defects at all discovered in the biliary system?

DR. CHARLES BARLOW: Actually, I think there were none.

DR. BENJAMIN BOSHES: I have seen some reports of congenital anomalies in the biliary system, but the brains were not studied, and I thought such correlative pathology may have been present here. I know of three children in one family who had this defect. All died shortly after birth, but no brain autopsy was permitted.

DR. CHARLES BARLOW: The biliary trees were quite normal. I wish to thank the discussants.

Electroencephalographic Studies on Children with Measles with No Clinical Evidence of Central Nervous System Involvement. DR. HERBERT J. GROSSMAN (by invitation), MRS. ERNA L. GIBBS, DR. HAROLD W. SPIES, and DR. MARK H. LEPPER.

A previous study has shown that definite abnormalities are present in measles encephalitis; these often persist after the clinical symptoms have subsided (H. J. Grossman and E. L. Gibbs). It seemed highly desirable to study cases of measles without clinical evidence of encephalitis. A series of 114 such patients were examined. About 50% had complicating bacterial infections. All were made afebrile with chemotherapy and/or salicylates before recordings were made. Forty-three of the patients had tracings which were definitely abnormal; among these, 14 had the classic extreme slow activity which is mostly seen in stupor. The abnormalities observed were qualitatively and quantitatively similar to those seen in measles encephalitis, but in most cases they cleared up much more rapidly; but in some cases they persisted. Usually the electroencephalogram returned to normal within one week. Among the 30 measles encephalitis patients previously studied, extreme slow activity (stupor pattern) lasted about four weeks, and 50% of the tracings were definitely abnormal even after six weeks.

Prolonged follow-up studies are being carried out on the group which had measles encephalitis, and we are also doing follow-up studies on the small group in the present series (measles without clinical evidence of encephalitis) who had persistent electroencephalographic abnormalities. Up to the present time one patient in this small series has developed seizures and a definite focus of electrical abnormality.

Abnormal electroencephalograms in the present group (measles and no clinical encephalitis) show an age distribution similar to that for measles encephalitis (clinically diagnosed). No abnormal tracings occurred in patients with measles who were less than one year of age. Bacterial complications did not increase the incidence of abnormality.

DISCUSSION

DR. JOSÉ M. R. DELGADO (by invitation): May I ask if you have controls, by which you know whether the electroencephalographic changes observed in measles are specific of the disease or nonspecific, being a result of the fever?

DR. HERBERT J. GROSSMAN: I do not believe these electroencephalographic abnormalities are specific of anything in themselves. They obviously have to be correlated with other clinical and laboratory findings. Certainly, the severe abnormalities described have not been observed in the tremendous number of normal controlled cases which Dr. and Mrs. Gibbs have collected over the years. Abnormalities have been observed in many disorders, among which is the group we have described having vague clinical manifestations of fever and an unusual degree of lethargy, which is currently under study.

Cerebral Mechanisms Possibly Related to Pain and Fear. DR. JOSÉ M. R. DELGADO, New Haven, Conn. (by invitation).

Peripheral noxious stimulation evokes in the monkey a typical pattern of response which includes defensive and offensive movements, screaming, and autonomic manifestations. We have experimented to learn which areas of the brain could produce a similar pattern. Monkeys and cats were studied for about a two-month period each, by means of permanently implanted multilead electrodes within the brain. In the monkey, electrical stimulation of the lateral part of the tegmentum, central gray matter, the posteroventral nucleus of the thalamus, the crus of the fornix, and the posterior part of the hippocampus elicited the typical pattern. Stimulation of other areas of the brain, including the sensorimotor cortex, did not evoke these reactions. In the cat the representation was similar. Electrical stimulation of the tectal area induced fighting against control animals, showing that the offensive reaction was purposive and well oriented. The fact that a similar pattern was induced by stimulation of the above-mentioned structures suggests a closed functional relationship. The so-called sensory cortex would have a less important role than the thalamus and the hippocampus in nociceptive, sensory integrations. In the cat it has been shown that the fear-like reactions

elicited by stimulation of cerebral structures had all the drive properties of true emotions and could be used to establish conditioned response, could motivate the trial-and-error learning and performance of an instrumental response, and could serve as punishment to teach hungry animals to avoid food.

DISCUSSION

DR. J. MASSERMAN: I need hardly say that we are appreciative indeed of Dr. Delgado's efforts, not only of the presentation tonight, but of his many years of stimulating thinking and research. Dr. Delgado mentioned my early experiments, but I do not think he is nearly as indebted to them as he implied. Even the briefest review of them will make this quite clear.

Some 15 years ago my colleagues and I, as part of what now seems an unnecessary attempt to disprove a concept, then rampant, that the hypothalamus was the seat of both the emotions and the soul, implanted electrodes into that much-punctured area. We found that its stimulation in cats produced only undirected, stimulus-bound sham rage, which could not be conditioned to external stimuli; on the othere hand, hypothalamic destruction temporarily disorganized the peripheral expression of affect, but did not impair the animal's capacities to react to external stresses. We, therefore, concluded that the hypothalamus was a region for the coordination of affective motor discharge, but not for motivation or emotional experience. Our negative results, therefore, bear in no immediate way on Dr. Delgado's work, since, happily, he places his region for the perception of pain and rage far away in the thalamus.

However, recent studies by Dr. Pechtel, Dr. Schriener, and myself, at Northwestern, University, raise a point on which I would appreciate Dr. Delgado's comment. We found that the effects of diencephalic lesions vary markedly with the previous experiences of the animal: For instance, a dorsomedial thalamic lesion renders a normal cat a little slow and stupid but leaves it relatively friendly, whereas the same lesion in a cat previously made experimentally neurotic frequently changes its disposition toward meanness and aggressivity. Also, Dr. Pechtel has found that retraining and other experiences immediately after operation can significantly change the effects of any lesion. So now the laboratory investigator is, with providential justice, brought face to face with a problem of which the clinician has long been aware: He must know not only the lesion he is studying, but also the previous experiences of the nervous system in which that lesion was produced. Will Dr. Delgado share our tribulations on that point?

DR. FREDERIC A. GIBBS: Many years ago (1936) my wife and I stimulated the brains of anesthetized cats with needle electrodes to find the brain areas which have the lowest convulsive threshold. In the course of this work we encountered certain areas where stimulation produced unmistakable evidence of intense pain. These lay in the lateral inferior thalamus, and the response was entirely different from that obtained from stimulation in other parts of the brain. I wonder whether Dr. Delgado has not seen some differences, either qualitative or quantitative, between pain reactions which followed thalamic stimulation and those that followed stimulation of the hippocampus.

DR. JOSEPH EVANS: I was struck in the movie by the apparent persistence of a memory when the posterior hippocampus was stimulated. I am thinking of work with which I know Dr. Delgado is familiar. Scoville has reported that posteromedial temporal lobectomy in the human may be associated with memory loss. I wonder whether there is reasonable evidence in contrasting the control lesions that destructive lesions in the posterior temporal region destroy memory.

DR. WARD HALSTEAD: If I may harken back to the period of Henry Head's work on sensation, I recall from my reading that he gave special emphasis to the area of the lateral masses, and when this was implicated by a lesion, there was the same sort of reaction in the patient as Dr. Gibbs has described in the cat. Henry Head described that in humans about 30 years ago. I wonder if there may not be on stimulation of the lateral mass of the thalamus in the cat the same effect which in the human we call unpleasantness, and it may have been no different from that when the motor cortex or similar areas were involved.

DR. JOSÉ M. R. DELGADO: In our opinion, the previous exposure of the animals to brain stimulation did not influence the subsequent experiments of conditioning, because each type of experiment was performed in a different room. In any case, the fact that in each cat "fear" responses were obtained only by stimulation of two or three cerebral points, and were not elicitable from the others, shows that the effect was specific.

With respect to the other questions raised by Dr. Masserman concerning retraining and recovery of the animals after destruction of some areas of the brain, I have experience gained in investigations performed in monkeys in collaboration with Dr. H. E. Rosvold. In these experiments, some areas of the frontal lobes or caudate nucleus were electrocoagulated through permanently implanted electrodes while delayed alternation tests were being performed. In this way it was possible to observe the immediate effects of the lesions, which in some monkeys impaired the performance of the test without possibility of relearning. With this method, undesirable delays in testing—necessary after surgical brain destruction —were avoided.

Dr. Halstead's comments and his information concerning pleasure reactions, were very interesting. I have made some studies, in collaboration with Drs. Hamlin, Higgins, and Mahl, of stimulation of the temporal lobe in patients with psychomotor epilepsy. In addition to some phenomenon of déjà vu, we have been able to observe the elaboration of thoughts with sexual content, which were probably evoked by specific temporal lobe stimulation. In these cases a simultaneous recording of the electrical activity of surface and depth of both temporal lobes through 18 channels was synchronized with a tape recording of the interview with the patients.

I agree that electrical stimulation of the dura could produce pain-like reactions. In some of our animals, which may be considered controls, pain-like reactions were evoked by electrical stimulation of the root of the trigeminal nerve. But the pain-like reactions evoked by electrical stimulation of the posteroventral nucleus of the thalamus, for example, seemed to be specific, and could not be explained by dural stimulation, because it was not evoked when stimulation was applied through other leads, closer to the surface.

I was very interested in Dr. Gibbs's comments concerning convulsive thresholds, because this is one aspect that we are investigating at present in unanesthetized monkeys, with permanently implanted electrodes. We have seen that thresholds to evoke postdischarges are constant through periods of months, and also that the pattern of postdischarge repeats itself with similar characteristics.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Morris B. Bender, M.D., Chairman, Section of Neurology and Psychiatry, Presiding

Joint Meeting, Jan. 11, 1955

Results of Anterior Choroidal Artery Occlusion in Parkinsonism. Dr. Irving S. Cooper.

It is the purpose of this presentation to present a follow-up study of the results of my personal experience with anterior choroidal artery occlusion in Parkinsonism. To this end, a motion picture is shown which demonstrates six Parkinsonian patients prior to operation, immediately after operation, and at follow-up periods varying from 3 to 24 months. These films demonstrate immediate postoperative relief of tremor and rigidity, without motor loss, in the extremities contralateral to operation. Persistence of this alleviation of tremor and rigidity and improvement in activities of daily living are demonstrated in the follow-up motion pictures.

In addition, six patients are presented in person who had been subjected to the anterior choroidal artery operation from 9 to 24 months previously. Each is demonstrated to have had alleviation of tremor and rigidity since operation. This documents the results recently described in a series of 50 consecutive operations of anterior choroidal artery occlusion.

DISCUSSION

Dr. John Arthur MacLean: I think we have all fallen into a fallacy in reading textbooks —anatomic, pathologic, and physiologic—that have been perpetuating anatomic inaccuracies.

Dr. Harry A. Kaplan: At Kings County Hospital a project has been carried out during the past 15 years concerned with the therapy for Parkinson's disease. In connection with this, a study of the distribution of the arteries of the brain has been pursued. Naturally, we were interested in the procedure described by Dr. Cooper for relief of disabilities associated with Parkinson's disease.

On six patients occlusion of the anterior choroidal artery was performed. Tremor and rigidity were substantially altered in only one of these. However, in this case, on emotional

stress the tremor would recur. In none of these patients was there any bilateral effect, such as improvement in posture or gait. In two patients tremor and rigidity ceased for 24 hours, then recurred with the same intensity as before operation.

A statement was made just now implying that the description of the distribution of the anterior choroidal artery, as recorded in textbooks, is inaccurate. With this I disagree. An artery may be occluded surgically at a single point, and the part distal to the site of occlusion, however, may still function by virtue of its collaterals. The anterior choroidal artery is no exception. It has many branches and receives collaterals from at least four different arteries. The branches of this artery, which usually supply a small area of the mesial portion of the medial part of the globus pallidus, are not constant, and this part of the brain may occasionally receive its blood supply from branches of the carotid artery itself, or in some instances from the middle cerebral artery. One of our patients who was subjected to occlusion of the anterior choroidal artery died six months later. At autopsy the surgical occlusion of the artery was found to be complete. The only lesion attributable to the occlusion was located in the most mesial inferior part of the globus pallidus and the immediate subthalamic area.

DR. IRVING S. COOPER: I have little to add. It is true that these results have not been confirmed in all series, although many neurosurgeons have done so. In my own hands, I have had some failures on a technical basis, where I failed to occlude the artery completely. Others, when they have a failure, should investigate such a possibility. I obtain an angiogram before the operation, and if the operation has failed, I take a postoperative angiogram. In some such cases we have been able to demonstrate that the artery is still open. Particularly in one's early experience, of five or six cases, as in Browder's experience, that point should be borne in mind. How often these good results can be reproduced I do not know, although the percentage is high in our own series. We have shown seven or eight patients in the moving pictures who are free of tremor or rigidity; in addition, the five patients who were personally presented show conclusively excellent results. If time had permitted, we would have had many more such results here. My purpose was merely to present in person these unequivocal facts and results. We must wait a longer time before concluding how often the results can be reproduced and how long the duration will be.

Psychological Study of Visual Auras in Patients with Brain Damage and Seizures. DR. THOMAS C. GUTHRIE (by invitation) and DR. AARON T. BECK (by invitation).

The five patients included in this investigation demonstrated evidence of gross structural disease of the temporal or occipital cortex. Associated with the brain damage were grand mal seizures, preceded by a visual aura. Each patient had a history of head injury and presented neurological deficits on examination and an abnormal electroencephalogram. In the study of these patients, psychiatric interviews, psychological tests, hypnosis, and free association amplified the neurological evaluation. It has been possible to reproduce the visual aura under hypnosis, without the seizure. When hypnotized, these patients revealed much fantasy material related to their visual hallucinations.

From these experimental data we have concluded that the visual aura, in the brain-damaged patient, not only is a manifestation of the patient's lesion, but also is related to the personality of the patient. The visual aura is an expression of the individual personality, similar to a dream, and employs psychological mechanisms, such as symbolization and distortion. The visual aura and, subsequently, the seizure occur at a time when certain threatening or disturbing life situations arise. The visual aura then is not formed exclusively by activity in a discrete area of cerebral cortex but is a complex phenomenon resulting from the total integrative activity of the brain.

DISCUSSION

DR. DONALD J. SIMONS: It would be interesting to know whether the treatment of the combat neurosis in the first patient made any change in the nature of the patient's seizures.

DR. STANLEY LESSE: It is interesting to note that these visual auras occurred in brain-damaged patients; in patients with nonorganic illness (schizophrenia) we have stimulated the temporal lobes in approximately 15 cases with use of local anesthesia, and we have not been able to reproduce any of the visual or hallucinatory material.

DR. THOMAS C. GUTHRIE: In answer to Dr. Simons' question, I would like to state that with psychotherapy and anticonvulsants the patients all improved. They had fewer seizures, but I could not make any statement as to which agent was responsible for the improvement.

Use of Large Doses of Cortisone in Schizophrenia. Dr. Phillip Polatin, Dr. Stanley Lesse (by invitation), and Dr. Meyer M. Harris.

This paper is published in full in the present issue of the Archives, p. 485.

DISCUSSION

Dr. Paul Goolker: We are all grateful for the facilities provided by the Psychiatric Institute for the testing and assaying of new drugs and methods of therapy, and for the way Dr. Polatin and his collaborators have utilized these facilities for our enlightenment. The study of the use of drugs, in addition to contributing to therapy, provides a means for the further understanding of psychic function, and this is just as important as the therapeutic measures that are applied.

Dr. Stanley Lesse: I would like to thank Dr. Goolker for his discussion of our paper. Dr. Goolker has offered many valid criticisms and questions: 1. We had too few cases; however, we had only a certain amount of drug to use. 2. Our choice of 500 mg. was not purely an abstract one. We had had a verbal communication from Cohen, in Cleveland, stating he had been using this dose, and he felt that with large doses he had obtained his best results. That was the reason we used this dose.

Group Psychotherapy in Patients with Peptic Ulcer. Dr. Aaron Stein.

In an effort to deal with the underlying emotional tensions which, according to present views, are thought to be similar in most patients with peptic ulcer, and which constitute one of the factors in the persistence of their symptoms, we treated a group of patients with chronic peptic ulcer for a period of 18 months with a psychoanalytically oriented type of group psychotherapy. All the patients were found to have severe underlying psychiatric disease with rigid, constricted personalities and poor object relationships. In 14 of the 15 patients the onset of ulcer symptoms seemed related to the loss or threatened loss of the mother or mother-surrogate.

Because of the supportive and tension-lessening factors operative in the group psychotherapy, all these rigid, constricted patients participated actively in the treatment. After working through their guilt over being ill, they were able, first, to express resentment over not being cared for, and then to verbalize their dependent needs. Slowly, the rigid, intolerant group attitudes changed to more tolerant and flexible ones, so that the patients could begin to develop more realistic relationships and more effective methods of satisfying their needs.

Of the 15 patients in the group, 12 continued in the group treatment. Three of these 12 were considered unimproved; the remaining 9 showed varying degrees of improvement, both psychiatrically and in their ulcer symptoms. The degree of psychiatric improvement in general tended to parallel the degree of improvement in the ulcer symptoms.

It was concluded that group psychotherapy appears to have definite usefulness in aiding patients in whom chronic peptic ulcer is associated with a regressed, rigid type of personality to participate readily in the psychotherapeutic process.

DISCUSSION

Dr. Jacob A. Arlow: Observation of 12 to 15 patients for a period of almost two years, with several years of ensuing follow-up, is a considerable psychotherapeutic experience. I doubt if the original studies which formed the basis for the psychodynamic formulations of peptic ulcer had a larger group of patients.

Concerning the selection of the patients, the following factor must be noted: Two sets of criteria were used, one furnished by the physicians, namely, the presence of peptic ulcer, and the other furnished by the patients, namely, their willingness to participate in a program of group psychotherapy. It would seem to me that at this point a very significant weighting was introduced into the sample.

The very high incidence of severe psychopathology (100%) in this group may be attributed to this unwitting deviation of a selection of patients in the direction of the emotionally ill. It is most doubtful that a random selection of ulcer patients in general medical practice would reveal them to be uniformly rigid, immature, dependent emotional cripples. In addition to the therapist's experience and skill (Dr. Stein has been pioneering in this field for many years), the receptiveness of the patients so selected is another factor that contributed to the truly impressive therapeutic results reported in this paper.

PHILADELPHIA NEUROLOGICAL SOCIETY

Alexander Silverstein, M.D., *Presiding*

Regular Meeting, Dec. 3, 1954

Subcortical Mechanisms in Epilepsy. Dr. A. Earl Walker and (by invitation) Dr. Orlando J. Andy, Dr. G. F. Poggio, and Dr. W. H. Faeth.

This study was carried out on monkeys, which were prepared with the local use of 0.5% procaine hydrochloride anesthesia, immobilized with curare, maintained on artificial respiration, and supported with intravenous dextran. Bipolar stimulations and recordings were made with a thyratron and two synchronized electroencephalographs, respectively. With the use of a stereotaxic instrument, numerous electrodes were simultaneously placed in various predetermined subcortical structures. Points of stimulation and recording were verified in histological serial sections of all brains.

Multiple subcortical and cortical recordings were made during convulsive activity induced by electrical and chemical stimulation of the motor cortex and amygdala-hippocampus complex. From the amygdala-hippocampus complex, the preferential pathways appear to be to the contralateral amygdala and hippocampus and to the ipsilateral anterior temporal cortex, hypothalamus, thalamus, caudate nucleus, putamen, and frontal granular cortex, although not necessarily in that precise order. From the motor cortex, the preferential pathways appear to be to the contralateral homologous motor cortex and the ipsilateral putamen, thalamus, brain stem nuclei, amygdala-hippocampus complex, and cerebellum.

DISCUSSION

Dr. James J. Ryan: I do not recall the name of the author mentioned by Dr. Walker, but I should like to ask whether the author meant that the removal of the globus pallidus in humans would stop seizures? If this is what he meant, was the statement backed up by experimental work? I should also like to know if these patients would not eventually show a picture somewhat similar to that we see in globus pallidus damage associated with carbon monoxide poisoning? I wonder whether these patients would not be worse off than before the procedure was done.

Dr. Henry T. Wycis: The question of eliminating subcortical structures in patients with abnormal seizure patterns is an interesting one. In 1951, Dr. Spiegel and I studied cases with both petit mal and grand mal seizures. We made simultaneous records of subcortical and cortical structures by means of stereotactically placed electrodes. There were three groups of recordings. 1. A group in which the discharge appeared first in the thalamus and then also in the frontal leads. The thalamic discharges outlasted those from the cortex. 2. A group somewhat similar to the cases mentioned tonight, in which the discharges appeared in the thalamus and in the cortex simultaneously. 3. Lastly, a group in which the discharges were recorded from various regions of the thalamus and subthalamus alone. Destruction of these foci by electrolysis resulted in improvement in two patients out of six, there being a reduction in the number of seizures. Since we were able to record these discharges in various subcortical structures, it was doubtful whether we could completely eliminate the seizures by isolated lesions alone.

I question Dr. Ryan's statement that there is likely to be an increase in hypertonicity in cases where lesions are made in the globus pallidus. In 12 cases of Parkinson's disease, where Dr. Spiegel and I made lesions in the region of the ansa lenticularis and/or pallidum, we did not find an increase in hypertonicity; in some of the cases there was a decrease, rather than an increase, in tone.

Dr. A. Earl Walker: We appreciate very much the comments of the discussers. We were stimulated to undertake this work by the observation that a patient, after a hemispherectomy for epilepsy, had attacks that were similar to those before the cortical removal. These were described as focal epileptic seizures but lacked the march of a typical Jacksonian phenomenon. However, they began in the arm and eventually spread to the entire body. Thus, the possibility of their arising in one or more of the various subcortical structures was entertained. Several laboratory experiments have given support to this concept. For example, we have a monkey which, after application of alum to the motor cortex, developed jerking of the contralateral extremities. Even after subsequent removal of the entire frontal and parietal cortex, the jerking persisted. I assumed the jerking came from one or more of the subcortical structures or the ipsilateral hemisphere.

In none of our observations on subcortical epilepsy have we seen typical petit mal attacks, such as were described by Dr. Wycis.

We were intrigued to find that preferential pathways were followed by the epileptic discharge. This suggests that they might be interrupted in an attempt to stop the propagation of the discharge. On the basis of the assumption that the seizure impulse spread through the globus pallidus, Hayashi and other Japanese surgeons have operated upon the basal ganglia in man, reporting that by removal of the globus pallidus one could eliminate the attacks. I do not think the problem is quite so simple. We found that an after-discharge which spreads to the various basal structures is not necessarily funneled through the globus pallidus. I doubt that these attacks can be eliminated by interruption of a small part of the circuit.

Pain Simulating Sciatica Due to Tumor (Hamartoma) of the Second Thoracic Cord Segment: Superiority of Testing Temperature Sensation over That of Pain Sensation for Accurate Cord Level Localization. DR. MICHAEL SCOTT.

The following case is reported because it shows that a tumor in the high thoracic cord can produce pain in the lower extremity and offer a diagnostic problem. It also illustrates what I and others have noticed, i. e., that frequently testing for temperature sensation, particularly for warm or cold, will give a more accurate level of the cord lesion than testing for pain sensation, the latter at times placing the lesion as many as six to eight segments below the true level.

REPORT OF A CASE

Patient, age 52, first examined on Dec. 8, 1947. She complained of burning pain in the left gluteal area, concomitant with waves of heat and pain throughout the left lower limb. "It is inside the limb and all the way through." She was awakened frequently at night by fleeting paroxysms of pain. She could not tolerate pressure against the left buttock from bedcovers or while sitting. If the pain occurred during urination, the patient could not continue but resumed micturition when it ceased. The past history was negative.

The neurological examination was negative except for decrease of the left Achilles reflex. All laboratory tests, the spinal fluid, spine x-rays, and air and Pantopaque lumbar myelograms were negative.

An extensive lumbar laminectomy done 13 months after onset showed no evidence of any extradural or intradural lesion. There was temporary improvement for three months, and complaints recurred.

The left sciatic nerve was explored elsewhere, with a diagnosis of "adhesion about the nerve." Again, there was temporary relief with recurrence. In August, 1952 (five and a half years after onset), weakness of the right leg developed. Examination by a neurologist at another institution revealed a Babinski sign on the right and a patchy decrease in sensation below T 11 on the left. He suspected an intramedullary tumor at this level, but a thoracic myelogram by the cisternal route was reported negative. The patient was readmitted to Temple University Hospital two months later. Examination showed a Babinski sign on the right. No definite level to pinprick. Complete loss of sensation on left below T 11 for the warm tube and below T 3 for the cold tube. Right side normal.

The Pantopaque myelogram showed a defect at T 2 (slide). Thoracic laminectomy (Jan. 17, 1953), seven and a half years after onset, revealed an inoperable intramedullary tumor (hamartoma) of the second thoracic cord segment [slide of tumor in site at operation and microscopic section shown]. Patient given x-ray therapy. Slight relief of pain and minimal progression of cord involvement observed two years later (Dec. 2, 1954).

CONCLUSIONS

1. An intramedullary tumor of the second thoracic segment of the spinal cord can produce pain limited to one lower extremity.

2. It may be impossible during the early stages to differentiate this pain from that due to lesions involving the roots of the cauda equina, or even the sciatic nerve.

3. A complete myelogram, including the thoracic and cervical areas, should be done if the fluoroscopic lumbar phase of the myelogram is negative or equivocal.

DISCUSSION

DR. FRANCIS GRANT: I was fascinated by this paper. I suppose you have an explanation. I have never encountered such a case. Why did the patient have that pain?

DR. MICHAEL SCOTT: Perhaps Dr. Walker could tell us why this high thoracic lesion caused the leg pain, which was burning, and not the classic sharp, shooting pain. I hoped that some of my colleagues here might give us their observations on stimulation of this tract.

Foerster states that in humans stimulation of the spinothalamic tract under local anesthesia at the thoracic level will produce pain in the contralateral lower extremity. I believe that such was the situation in the present case.

DR. CHARLES RUPP: Dr. Walker, have you any thoughts that might clear up this mysterious case?

DR. A. EARL WALKER: I'm afraid I can't clear up the mystery, but I am very much interested in the phenomenon of burning pain. It occurs not only with peripheral lesions but also with spinal cord, medullary, thalamic, and even cortical lesions; so it is not possible to make a differential diagnosis on the type of pain alone. I wondered whether this burning pain might be connected with irritation of the posterior columns. It comes to mind that Jefferson Browder did a section of the posterior column for such pain associated with phantom limb, with some success. In my rather limited experience, stimulation of the spinothalamic tract in the spinal cord has induced pain, but thermal sensations are reported in 37% of cases by Drs. White and Sweet, who have a much more extensive experience. Although burning pain is usually considered of sympathetic origin, it is not always relieved by section of the chain. Perhaps it may be related to spinal cord sympathetic pathways.

DR. TEMPLE FAY: I recall one case of a curious syndrome. The patient had been to some 30 physicians, with a symptom complex of referred pain to the left leg and sharp, shooting pain in the right side of the face upon turning her head to the right. Dr. Frazier diagnosed the facial condition as trigeminal neuralgia. Another physician had diagnosed the leg pain as Buerger's disease. Some five years later, when I saw her, I found signs of a high cervical lesion. Planographic films showed an almond-shaped calcification at the level of the foramen magnum. I removed an almond-shaped, calcified meningioma on the right side of the cord at the foraminal level, giving this phenomenon of trigeminal descending root pain to the right and crossed projection of pain to the left leg when the head was turned. She recovered and was symptom-free. This may throw some light on what the spinothalamic tract can do by local irritation.

DR. HENRY T. WYCIS: Dr. Joseph Evans referred to us a case in which he removed a very extensive acoustic neurinoma. Part of the tumor extended to the foraminal level. Postoperatively, dysesthesia developed on the side opposite the tumor removal. The patient refused mesencephalotomy because of the possibility of impairment of hearing, in view of the already existing unilateral deafness following removal of the tumor. Dr. Evans felt that a section of the posterior columns might help.

DR. MICHAEL SCOTT: Craig and his associates have reported that tumors as high as the 10th thoracic segment can produce sciatic pain. Because of this, and the findings in the present case, we now insist that the Pantopaque be carried up the entire spinal canal, including the cervical area, if the lumbar phase of the fluoroscopic examination does not show a very definite lesion.

Clinical Survey of British Methods for Treatment of Spastic Patients. DR. TEMPLE FAY.

In London, various programs of treatment have been developed for the treatment of "spastics" (cerebral palsy patients), chiefly based on American methods. Patients treated were the less severe types, the more difficult problems being classified as "mentally deficient," institutionalized, or not eligible for rehabilitation therapy.

Striking results were noted from the "Collis technique," in which therapy is reinforced by "motivation" and "achievement." Remarkable improvement by the use of hemispherectomy in epileptic hemiplegic patients was reported by Mr. McKissick (National Hospital, Queen's Square), approximately 80% of a series (35) being benefited. Those examined showed improvement in motor facility and coordination; however, total loss of skilled, sensory, and visual components occurred on the involved side.

Centers in Birmingham and Bristol presenting individual types of orientation to the problem of "spastic" paralysis were well organized. Mr. Pollock (Edinburgh) has developed advanced methods of corrective orthopedic surgery, with physical therapy and neuromuscular patterns of movement, as aids in solving difficult motor aspects of the problem.

Diagnostic and therapeutic measures in the United States are in advance of those of British clinics. Motivation appears to have given greatly improved end-results. Screening panels of various specialties are developing around physical medicine. Progressive planning of patient rehabilitation is becoming more widely established.

DISCUSSION

DR. HENRY T. WYCIS: Dr. Fay's point, that this difficult problem cannot be answered by one person, but can only be solved by a team working together, is a good one. This may be the answer. From our own standpoint, we have been interested in the athetoid group, to see what cortical structures are at fault in the production of abnormal movements. We began planting electrodes in the subcortical structures of these abnormal children and recording from them.

Our problem at present seems to be the production of a stereotaxic atlas for children. The one for adults was five years in the making. With production of an atlas for children, we may be able to help some by operation, although training will still be an important part of treatment.

DR. NATHAN S. SCHLEZINGER: I was intrigued by a comment of Dr. Fay's, in which he referred to cerebral palsy as extending from pediatrics to geriatrics. I am not quite sure what he meant by the latter. I am inclined to caution in using the term "cerebral palsy" to cover a great number of neurological problems. I saw a case in consultation at one of the hospitals of this city, and it was labeled "cerebral palsy." Examination indicated that there was progressive hemiplegia in a patient who was approximately 60 years of age. The ultimate diagnosis was brain tumor. We have to be cautious in using this term "cerebral palsy," which may obscure, rather than clear up, certain diagnostic problems.

DR. E. A. DENBO: Were the British clinics doing routine pneumoencephalograms in these cases?

DR. TEMPLE FAY: Yes. One team is in Bristol and one in London for screening lesions suitable for hemispherectomy. There is more pneumoencephalography being done than before.

With reference to the term "cerebral palsy": I have felt for 10 years that we have plenty of terms to fit cerebral pathology, but we have very little chance of stopping popular use of the term "cerebral palsy." Most people think of cerebral palsy as occurring only in children, but this is no longer true. The term "cerebral palsy" includes any motor defect, at any age, and I am afraid it may include some psychomotor defects as well. They have included the geriatric group, as well as some types of spasticity found in cerebral palsy at birth. This field really belongs to neurology. The orthopedic men have pioneered it, and the pediatricians have taken over part of it, but we organic neurologists should not just sit by and do nothing. I hope that some of our younger men will not scorn this chronic field of paralysis, as the older men have. There will be plenty of demand in the near future for diagnostic and neurosurgical corrective work in this new field of rehabilitation.

DR. CHARLES RUPP: I was happy to hear Dr. Fay say that the English group recognized the importance of the mental deficiency element in cases of cerebral palsy. We are inclined to dwell more on the motor defect and disregard the fact that there is also an intellectual deficit which militates against what we hope to do therapeutically. I am also pleased to know that in England the neurologist is included as part of the therapeutic team. Hereabouts, cerebral palsy has become a stepchild of the orthopedist, neurosurgeon, pediatrician, psychiatrist, social worker, and practically everyone but the neurologist. Dr. Bronson Crothers used to say that the most important thing in these cases was to evaluate the neurologic residuum. All attempts at therapy for the palsied child depend on developing the neurologic residuum, so as to attain maximum efficiency with what is available. The neurologist can assist a great deal from this standpoint.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

QUANTITATIVE HISTOCHEMISTRY OF BRAIN: III. AMMON'S HORN. O. H. LOWRY, N. R. ROBERTS, K. Y. LEINER, M. WU, A. L. FARR, and R. W. ALPERS, J. Biol. Chem. **207**:39, 1954.

Six histologically distinct layers of the cornu Ammonis of rabbits have been analyzed for protein, lipid and various of its fractions, riboflavin, and six enzymes. Small pyramidal cells are much lower in total lipid than the remainder of the brain, and in general composition are similar to the cells of the kidneys. Dendrites are as rich as cell bodies in metabolic enzymes and contain goodly quantities of lipid as well. These lipids may be around, rather than in, the cytoplasm of the dendrites. In confirmation of other work, lipids of the myelinated fiber are relatively rich in sphingomyelin and cholesterol. The high enzyme and acid-soluble phosphorus contents of the myelinated layers suggest that myelin is metabolically active.

PAGE, Cleveland.

STUDIES ON THE FATTY ACID OXIDIZING SYSTEM OF ANIMAL TISSUES: V. UNSATURATED FATTY ACYL COENZYME A HYDRASE. S. J. WAKIL and H. R. MAHLER, J. Biol. Chem. **207**:125, 1954.

Oxidation of fatty acids results during the first dehydrogenating step in an unsaturated fatty acyl CoA derivative, while the substrate for the second dehydrogenating step is a beta-hydroxyacyl compound. The two oxidation enzymes are linked by an enzyme catalyzing the reversible hydration of alpha-, beta-, and beta, gamma-unsaturated fatty acyl derivatives of CoA. The name unsaturated fatty acyl coenzyme A hydrase is suggested for this enzyme, since it is specific for unsaturated acyl derivatives of CoA. It has been isolated from beef liver mitochondria. Hydrase is activated by GSH (reduced glutathione) and cysteine and inhibited by *p*-chloromercuribenzoate, iodacetamide, and iodosobenzoate.

PAGE, Cleveland.

PRECURSORS OF SPHINGOSINE IN BRAIN TISSUE. D. B. SPRINSON and A. COULON, J. Biol. Chem. **207**:585, 1954.

Studying the synthesis of brain sphingosine ($C_{13}H_{27}.CH=CH.CHOH.CHNH_2.CH_2OH$) by isotopic methods, Sprinson and Coulon found that carbon atoms 3 and 2 and nitrogen of L-serine-3-C^{14}-2,3-D,N^{15} are utilized for carbon atoms 1 and 2 and nitrogen of sphingosine, respectively, while the carboxyl group is lost. Ethanolamine is not used for this portion of the molecule, while the alpha carbon and nitrogen of aminoacetic acid are incorporated almost surely by way of serine. Ethanolamine is utilized for C-3 to C-18 of sphingosine; fatty acids and cholesterol, via conversion to acetate.

PAGE, Cleveland.

EFFECT OF ACETALDEHYDE ON THE SYNTHESIS OF ACETYLCHOLINE, ACETOIN, AND CITRIC ACID IN RAT BRAIN PREPARATIONS. J. F. BERRY and E. STOTZ, J. Biol. Chem. **208**:591, 1954.

Acetaldehyde is not a normal intermediate in metabolism but occurs in blood while alcohol is being broken down and after administration of disulfiram (Antabuse). Berry and Stotz found that it increased the synthesis of acetylcholine and 3-hydroxy-2-butanone (acetoin) and decreased the formation of citric acid from pyruvate or acetate by rat brain homogenates and extracts of rat brain acetone powders. It also supported some acetylcholine and citric acid synthesis when used as the sole acetyl donor. Some evidence suggested conversion of acetaldehyde to acetyl-coenzyme A by a coenzyme-A-dependent reaction not requiring adenosinetriphosphate (ATP) or diphosphopyridine nucleotide (DPN). ATP, coenzyme A, and acetate are involved in acetoin synthesis, while hydroxylamine reduces it.

PAGE, Cleveland.

5-Hydroxytryptophan Decarboxylase: Preparation and Properties. C. T. Clark, H. Weissbach, and S. Udenfriend, J. Biol. Chem. **210**:139, 1954.

Hog and guinea pig kidney contain an enzyme which catalyzes the decarboxylation of 5-hydroxytryptophan to yield serotonin (5-hydroxytryptamine) and CO_2. The enzyme is specific. The decarboxylase is present in relatively large amounts in liver and stomach as well.

Page, Cleveland.

Effect of Theiler's GD VII Virus on the Intracellular Distribution of Radiophosphorus in Mouse Brain in Vitro. K. Moldave, J. Biol. Chem. **210**:343, 1954.

One-day-old minced mouse brain in which Theiler's GD VII virus was propagating exhibited increased uptake of $P^{32}O_4$ into the phospholipid of all "cellular fractions." The most marked effect of the virus was stimulation of $P^{32}O_4$ incorporated into the protein and nucleic acid fractions of the smallest particulate fraction.

Page, Cleveland.

Localization of Cerebral Electrical Activity: The Acoustic Cortex of Cat. E. R. Perl and J. U. Casby, J. Neurophysiol. **17**:429 (Sept.) 1954.

Perl and Casby present their method for the localization of cerebral electrical activity by utilizing the Laplacian of the surface potentials (a measure of the current rising perpendicular to the surface) with an array of five electrodes. The auditory area of the cat was activated by "click" stimulus. The distribution of the Laplacian field was regularly more restricted than the comparable monopolar field. Laplacian responses were consistently present in the region bounded anteriorly and superiorly by the suprasylvian sulcus, inferiorly by a line from the tip of the anterior ectosylvian sulcus to a point several millimeters below the tip of the posterior ectosylvian sulcus, and posteriorly by the posterior ectosylvian sulcus. Inferior to this region, a strip across the anterior and middle ectosylvian gyri showed variable degrees of Laplacian activation. The area delineated by the click-evoked Laplacian activity was divided into four areas, A_I, A_{II}, A_{EP}, and a portion of S_{II} (following Rose and Woolsey). The first region was stable, lying in the dorsal portion of the anterior and middle ectosylvian gyri. The extent of this regularly active area was remarkably similar to that defined by other workers as the cortical projection of the medial geniculate body. A_{II} and A_{EP} were located in a belt ventral to A_I and were more difficult to activate. Responses to clicks were also found in the leg area of the second somatic projection. There appeared to be general agreement as to the extent and location of the subdivisions delineated by this method and the detailed cytoarchitectural analysis of the auditory cortex of the cat.

Siekert, Rochester, Minn.

A Differentiation Between Red and White Muscle in the Cat Based on Responses to Neuromuscular Blocking Agents. P. A. Jewell and Eleanor J. Zaimis, J. Physiol. **124**:417, 1954.

The mode of action of decamethonium on neuromuscular transmission was studied in the "red" and "white" muscles of the cat; tibialis was used as a typical white muscle and soleus as a typical red muscle. Decamethonium blocks neuromuscular transmission in tibialis (white muscle) by causing persistent depolarization; no other action was found. It was found to have a twofold action in tibialis, a primary depolarizating action, and a secondary action based on competition with acetylcholine, in this last respect resembling the action of curare. In denervated tibialis successive doses of decamethonium caused a progressive depression of the directly excited twitch, suggesting a direct action on the muscle fiber.

Thomas, Philadelphia.

Changes at the Neuromuscular Junction of Red and White Muscle Fibres in the Cat Induced by Disuse Atrophy and by Hypertrophy. P. A. Jewell and Eleanor J. Zaimis, J. Physiol. **124**:429, 1954.

The effects of atrophy and hypertrophy on the mode of action of decamethonium on neuromuscular transmission was studied in the tibialis, a white muscle, and the soleus, a red muscle, of the cat. Disuse atrophy was brought about by tenotomy of the affected muscle and hypertrophy by tenotomy of the muscles synergistic with the affected muscle. Atrophied tibialis and

soleus responded to decamethonium like normal tibialis; i. e., neuromuscular block was due solely to persistent depolarization. The blocking action due to competition with acetylcholine, seen as a secondary effect in normal soleus, was not present in the atrophied red muscle.

THOMAS, Philadelphia.

Neuropathology

MYELOMALACIA AND MULTIPLE CAVITATIONS OF SPINAL CORD SECONDARY TO ADHESIVE ARACHNOIDITIS: AN EXPERIMENTAL STUDY. R. L. MCLAURIN, O. T. BAILEY, P. H. SCHURR, and F. D. INGRAHAM, A. M. A. Arch. Path. **57**:138, 1954.

The authors describe an experimental method for producing chronic adhesive arachnoiditis in dogs by the intracisternal injection of ethyl iodophenylundecylate (Pantopaque) or kaolin with the two agents injected in the same animal in 13 cases. They trace the pattern of spinal cord reaction resulting from this condition. They discuss the relation of the experimental findings to syringomyelia, chronic adhesive arachnoiditis, and vascular lesions of the spinal cord in clinical material. When the brains and spinal cords of these animals were studied, the resulting arachnoiditis was found to lead to communicating hydrocephalus, and also myelomalacia. Microscopic examination showed an adhesive arachnoiditis completely surrounding the spinal cord in all animals. The changes leading to cavitations began abruptly, and the process of degeneration and cavitation was most marked in the cervical region but occasionally extended well into the thoracic portion of the cord. When cavitations appeared, they usually extended to produce necrosis and rupture of the ependyma. From the histologic material the impression was gained that ischemia led to necrosis of the spinal cord, which extended to include the ependyma of the central canal posteriorly. This provided free access of cerebrospinal fluid into the area of necrosis through the defect in the ependyma.

N. W. WINKELMAN, Philadelphia.

PATHOLOGY OF THE BLOOD VESSELS IN MULTIPLE SCLEROSIS. G. MACCHI, J. Neuropath. & Exper. Neurol. **13**:378 (April) 1954.

Macchi believes that the blood vessels undoubtedly play a role in the pathological process of multiple sclerosis. He does not agree with those authors who deny the presence of such vascular changes or attribute no importance to them. On the other hand, he does not agree with those pathologists who assume that the prime factor of the disease is an inflammation of the blood vessels.

He describes the chronological vascular changes in the process of demyelination as follows: The first appearance of the demyelination is immediately marked by engorged venules and capillaries, and this may be due to a vasoparalytic action brought about by substances which originate in these areas of demyelination. The drainage of fat and noxious substances causes vascular and perivascular reactions. The accumulation of fat and fat-laden macrophages in the perivascular spaces and in the adventitia also retards the normal drainage. Then proliferation of the adventitia and new formation of vessels occur, and later perivascular and pericapillary infiltration of round cells is seen. These latter conditions are caused by the formation of diapedetic and angiotrophic substances, which, by spreading along the perivascular spaces, may produce isolated perivascular exudation distant from demyelinated plaques.

Concerning the perivenous arrangement of some plaques of white matter, a satisfactory explanation may be that the perivenous spaces are destined to drain the products formed by demyelinating foci.

The author believes that the demyelination is the primary and fundamental characteristic pattern of the disease and that stasis and congestion of the veins and capillaries at first accompany and then facilitate the demyelination. The other vascular and perivascular changes are secondary to the demyelination.

SIEKERT, Rochester, Minn.

Psychiatry and Psychopathology

ROENTGEN STUDIES OF THE EFFECTS ON THE SMALL INTESTINE FROM EMOTIONAL DISTURBANCES. J. FRIEDMAN, Am. J. Roentgenol. **72**:367 (Sept.) 1954.

An abnormal pattern of the barium-filled small bowel has been demonstrated in a large number of apparently unrelated conditions. This abnormal small bowel pattern has been called "disordered motor function" by Golden. It can be caused by disturbances of nutrition, by organic

disease in the intestine or mesentery, by administration of certain foodstuffs, or by drugs, or it can be associated with generalized metabolic disease, neurologic disease, allergy, or emotional disturbances. An abnormal small bowel pattern has been demonstrated frequently to be associated with various emotional disturbances. Friedman reports the histories of four patients in whom the small bowel pattern was normal during the beginning of the examination and then became abnormal after a discussion of emotional problems while the patient was on the fluoroscopic table. A striking change occurred in the appearance of the small bowel in all. In only one of the four cases was the abdominal symptom for which the patient was sent for study reproduced. The factors which produce the roentgen appearance of disordered motor function in the small bowel seem undoubtedly to have a relationship to the emotions. It is not possible to conclude from this study that we necessarily are supplied with an explanation of the patient's symptoms. The change in the small bowel appearance may not be caused by the same process that produces the symptoms. The altered small bowel pattern may not necessarily be a pathologic finding but may be a functional variation within normal limits, such as blushing in the skin of the face.

WEILAND, Grove City, Pa.

Meninges and Blood Vessels

A STUDY OF EIGHT SURGICALLY TREATED CASES OF SPONTANEOUS SUB-CORTICAL HAEMATOMA. A. WERNER, J. Neurol., Neurosurg. & Psychiat. **17**:57 (Feb.) 1954.

Eight cases of spontaneous subcortical hematoma treated by craniotomy and evacuation of the cavity are presented. In seven instances no etiological factor could be found; in one case arteriosclerosis may have played a part. The clinical picture consists mainly of the sudden onset of excruciating unilateral headache, followed by vomiting and impairment of consciousness, then spontaneous recovery from the initial stroke, with unilateral neurological disability on the side opposite the headache. As an aid in confirming the diagnosis, further investigations include lumbar puncture, to show fresh subarachnoid hemorrhage; arteriography, to eliminate a ruptured aneurysm and to show a vascular intracerebral space-occupying lesion, and pneumoencephalography, to confirm the exact location of the lesion. In half the cases reported it disclosed an air-filled cavity communicating with the lateral ventricle.

The author discusses the etiology and pathogenesis of these nontraumatic, spontaneous subcortical hematomas. In his opinion this condition has to be treated like any other subcortical space-occupying lesion, by complete removal. In these eight cases an osteoplastic bone flap was turned, the cortex incised or excised, and the cavity explored and emptied. There was one postoperative death, recovery of the seven other patients being fair to very good. The prognosis in these cases depends a good deal on the localization of the subcortical hematoma. If such cases are recognized and treated adequately, there is not as much danger in the immediate future to life as there is to function.

ALPERS, Philadelphia.

THROMBOSIS OF THE BASILAR ARTERY IN A CASE OF PREMATURE ARTERIOSCLEROSIS. Y. POURSINES, J. ALLIEZ, J. ROGER, and R. NAQUET, Rev. neurol. **89**:356, 1953.

This report concerns a 46-year-old alcoholic man whose complaints consisted of the sudden onset of headaches, diplopia, and tinnitus. There were also episodes of vertigo with falling to the right, attacks of dysphagia, and periods when sensation of the right side of the face and left side of the body was diminished. The blood pressure was 170/80. Following one episode of the above symptoms, there were observed a right Horner syndrome, nystagmus, hypesthesia on the right side of the face, and right-sided facial weakness and deafness. The left extremities and trunk were hypesthetic. There were signs of cerebellar dysfunction. Subsequently there developed right hemiplegia, followed in three days by left-sided hemiplegia and an associated sixth nerve palsy. The patient became febrile and cyanotic and died three weeks after the onset of symptoms. The antemortem diagnosis was thrombosis of the basilar artery. Postmortem examination revealed a marked narrowing of the lumen of the basilar artery. Atheromatous plaques were evident along the entire length of the basilar artery but did not extend beyond it. The smaller vessels showed no significant atheromatous involvement, but secondary thrombi from the basilar artery extended into the vertebral and posterior cerebral arteries. There were asymmetrical bilateral softenings of the base of the pons and of the cerebellum. There were also some minute softenings in the optic radiations, corpus callosum, and anterior commissure.

BERLIN, New York.

Diseases of the Brain

CASE-FINDING OF HANDICAPPED CHILDREN, WITH SPECIAL REFERENCE TO CEREBRAL PALSY. H. M. WALLACE, M. LENDING, H. RICH, and E. M. GOLD, A. M. A. Am. J. Dis. Child. **88**:298 (Sept.) 1954.

Wallace and her associates discuss one of the problems in the administration of a program for handicapped children, namely, that of early case finding. It is apparent that if handicapped children are to be absorbed into the regular community as quickly as possible, early case finding is the first step. In 1952 a follow-up study was done on those children reported in 1948 on the live-birth certificates to have selected birth injuries or congenital malformations. A questionnaire was prepared and sent to parents. Follow-up information was available on approximately 70% at the end of this four-year period. Of the group followed, 40% were known to have died, 24% were normal, and 6% were handicapped. No follow-up information was obtained on 30%. Of the group of 16 handicapped children, only 5 had been known previously to the Bureau for Handicapped Children. The incompleteness of voluntary reporting of handicapped children to a crippled children's agency is thus illustrated. In the present study the incidence of cerebral palsy was 19.8 per 1000 live births.

It was also noted in the study that the children who subsequently died had the highest percentage of short gestation. The death group also had the highest percentage of abnormal pregnancies. These factors, however, were not statistically validated in the study.

To the infants previously visited by the public health nursing home-visiting program, another group of newborn infants has been added. Included are those babies with birth injuries or congenital malformations as reported on live-birth certificates. It would also appear desirable to enlarge the scope of the paranatal problem from the present one of fetal and neonatal deaths to include those handicapping conditions which may be thought traceable to prenatal and natal causes.

SIEKERT, Rochester, Minn.

HYDROCEPHALUS CONSEQUENT TO CRANIUM BIFIDUM. W. R. CHAMBERS, A. M. A. Am. J. Dis. Child. **88**:466 (Oct.) 1954.

The mechanism of hydrocephalus as a complication in cranium bifidum is not obvious. Congenital atresia of the aqueduct and other associated abnormalities have been offered as explanations. A case is presented in which an hemangioma was discovered underlying the cranial defect. In this child an irregular protrusion in the midfrontal area was repaired in the neonatal period. At 3 months of age, however, the head was enlarged, and by 2 years of age he was thought to be hydrocephalic. A ventriculogram revealed normal-sized ventricles with no abnormality in position or shape except for the unusual distance between the anterior horns of the lateral ventricles and the frontal bone. A craniotomy was performed, and an intracranial tumor was found. The pathologic diagnosis was hemangioma. The inference is drawn that in certain cases intracranial exploration may reveal benign tumor associated with cranium bifidum, which either is responsible for the progressive enlargement of the head or else has secondarily blocked the cerebrospinal fluid system.

SIEKERT, Rochester, Minn.

DISAPPEARANCE AND MIGRATION OF EPILEPTIC FOCI IN CHILDREN. E. L. GIBBS, H. W. GILLEN, and F. A. GIBBS, A. M. A. Am. J. Dis. Child. **88**:596 (Nov.) 1954.

Although generalized epileptic disorder in the electroencephalogram is more or less characteristic of young ages, epileptic foci do occur in the very young. The characteristic focus in these is an occipital focus; older children are more likely to have a midtemporal focus. Forty-five children, who before 9 years of age had occipital lobe foci, were restudied after their ninth birthday. In 40% the focus had disappeared, and the electroencephalogram was normal; these were seizure-free. Twenty-three per cent still had an occipital lobe focus; 18% had now an occipitotemporal focus; 14% now had a midtemporal focus, and 5% had developed 14- and 6-per-second positive spikes.

Ninety-eight patients who were known to have a midtemporal focus were restudied after the age of 15 years. In 53% the record was normal; 9% still had a temporal lobe focus; 15% now had an anterior temporal focus; 23% had developed 14- and 6-per-second positive spikes.

Thus, with increasing age, focal seizure activity tends to disappear or to move into the site that is characteristic for seizure activity at the age which the patient has attained. The clinical seizure commonly changes to that usually associated with the other area.

SEIKERT, Rochester, Minn.

STUDIES IN TRAUMATIC EPILEPSY. W. R. RUSSELL and C. W. M. WHITTY, J. Neurol., Neurosurg. & Psychiat. **16**:73 (May) 1953.

This study is concerned with the analysis of the various features observed in spontaneously occurring focal fits following wounds of the sensorimotor cortex. Eighty-five cases of focal motor and somatic fits were studied.

The observations reported are in some ways complementary to the observations on cortical stimulation by Foerster, Penfield, and others. The variety of sensation, movement, and inhibition is as great in the spontaneously occurring fit as in fits obtained by cortical stimulation.

The authors state that, considering only marked and clearly defined differences in type of aura, at least five motor and seven sensory varieties can occur. They consider the relation of the site of injury and the sensorimotor deficit to these auras, and the direction of spread from one type of aura to another. They discuss the anatomical and physiological implications of their study.

Although broad anatomical divisions of the sensorimotor cortex do appear to be maintained for the different qualities and bodily sites of epileptic response, Russell and Whitty's findings do not suggest that these can be rigidly determined by this form of study. The impression is one of flexibility of cortical response. Such a veiw is in agreement with both the general trend of present neurophysiological work and with the results of cortical stimulation in man, where precortical or postcentral sites may each give rise to sensory or motor responses.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

CASE REPORTS OF PROGRESSIVE INFANTILE MUSCULAR ATROPHY (WERDNIG-HOFFMANN) IN FRATERNAL TWINS. R. H. LEYRER, A. M. A. Am. J. Dis. Child. **88**:604 (Nov.) 1954.

Leyrer reports two cases of infantile muscular atrophy (Werdnig-Hoffmann type) occurring in fraternal twins. Biopsy of the gastrocnemius muscle of both infants showed evidence of diffuse atrophy compatible with a diagnosis of muscular atrophy. Autopsy studies are not reported. The only, and older, sibling was affected with amyotonia congenita (Oppenheim's disease) (clinical diagnosis).

SIEKERT, Rochester, Minn.

LYMPHOMAS OF SPINAL EPIDURAL SPACE. J. G. LOVE, R. H. MILLER, and J. W. KERNOHAN, A. M. A. Arch. Surg. **69**:66 (July) 1954.

In the Mayo Clinic, 39 cases of spinal epidural lymphoma were observed without clinical evidence of involvement elsewhere in the body. It is possible that some of these lesions may develop primarily in the spinal extradural space. The lymphosarcoma of small cell type was most frequently encountered (14 cases). The reticulum cell sarcoma (11 cases) and Hodgkin's tumor (7 cases) were less common. Epidural lymphomas were prevalent in males (69%); they occurred in all age groups. The clinical symptomatology was that of extradural spinal cord tumor without pathognomonic features which would permit one to make the preoperative diagnosis of lymphoma. A bone erosion, visible on plain roentgenograms of the spine, was present in 33% of the cases. A spinal subarachnoid block was demonstrated in 93%.

All 39 patients were operated on, with 62% showing improvement; 36 patients received postoperative roentgen ray therapy, with only 31% showing additional improvement thereafter. Nitrogen mustard and cortisone had been also used, with symptomatic relief. Among the patients who were improved by surgery, 18 had recurrent symptoms within 1 to 48 months, but responded to additional roentgen ray therapy.

The ultimate outlook for spinal epidural lymphoma is poor. At the time of this survey 22 of the 39 patients had died. The total duration of the illness varied from three months to eight years. Fourteen patients were alive 1 to 18 months after the operation. Patients with reticular cell sarcoma seemed to have a longer survival time than those of the other groups.

LIST, Grand Rapids, Mich.

Peripheral and Cranial Nerves

ISCHAEMIC LATERAL POPLITEAL NERVE PALSY. F. R. FERGUSON and L. A. LIVERSEDGE, Brit. M. J. **2**:333 (Aug. 7) 1954.

Ferguson and Liversedge present nine cases of foot drop associated with a local vascular abnormality, either thrombosis or embolism of the femoral or popliteal artery. These cases illustrate the vulnerability of the lateral popliteal nerve to ischemia and indicate the predominance of motor involvement over sensory signs. The prognosis of the local process is good, complete recovery being likely and partial recovery the rule. The most satisfactory treatment consists in provision of a light elastic toe-raising spring during the period of paresis.

ECHOLS, New Orleans.

RECURRENT PERIPHERAL-NERVE PALSIES IN A FAMILY. D. M. DAVIES, Lancet **2**:266 (Aug. 7) 1954.

The author reports the occurrence of isolated peripheral nerve palsies in three members of a family, some of the attacks being of unknown cause, others following minimal trauma.

The father and son had recurrent attacks; the daughter, only one episode. The father's difficulty began when he was 20 years old, with sudden right foot drop and numbness of the outer side of the leg. This cleared in three months but recurred five years later. When he was 55 years old, he developed numbness of the side of his head after resting his forehead on the table for several minutes. Three years later he had a sudden wrist drop, which lasted two weeks. He also had recurrences of the right leg weakness. The son had similar recurrent isolated involvement of his right little finger and his left foot, which cleared. The daughter had weakness of the right foot, which lasted two months.

Other relations may have been affected, but the evidence of this was uncertain.

MADOW, Philadelphia.

Treatment, Neurosurgery

USE OF CHLORPROMAZINE IN CHRONIC ALCOHOLICS. J. F. CUMMINS and D. G. FRIEND, Am. J. M. Sc. **227**:561 (May) 1954.

The value of chlorpromazine in suppressing the nausea and vomiting that results from the ingestion of disulfram in the presence of alcohol was investigated in 60 patients with acute or chronic alcoholism. Patients were given 500 mg. of disulfram and 100 mg. of chlorpromazine. Twenty-four hours later they were given 500 mg. of disulfram and 50 mg. of chlorpromazine, and the following day, 500 mg. of disulfram and 25 mg. of chlorpromazine. Thereafter the patient was given 500 mg. of disulfram daily for one week. It was found that chlorpromazine suppressed the nausea and vomiting of the disulfram-alcohol reaction and prevented the postalcoholic agitation. The patients were able to take food in 24 hours after institution of the regimen, and many patients returned to work in 72 hours. Chlorpromazine alone was not as effective in stopping the alcoholism or relieving the agitation. The combination of disulfram and chlorpromazine eliminated the need for a "drying-out" period prior to the administration of disulfram.

BERLIN, New York.

DIABETIC NEUROPATHY: CONTROLLED THERAPEUTIC TRIALS. C. R. SHUMAN, Am. J. M. Sc. **227**:612 (June) 1954.

The "double-blind" technique of study was used in evaluating the therapeutic effectiveness of vitamin B_{12}, pregnant mammalian liver, and adenosinetriphosphate with thiamine in diabetic peripheral neuritis. Of 37 patients with diabetic neuropathy, about two-thirds failed to improve with a program of metabolic control. The latter were the subject of the investigation. One group was given injections of 10 to 1000γ of vitamin B_{12}. Pregnant mammalian liver was given daily for 10-14 days and then twice weekly for 4-6 weeks. Six subjects received 25 mg. ATP with 20 mg. of thiamine intramuscularly twice daily for two to four weeks. The best results were obtained with careful diabetic control. In those cases is which there were residual neuritic disturbances there was no alteration in the objective manifestations of the neuropathy with the use of the agents employed.

BERLIN, New York.

EXPERIENCES IN THE RADIATION THERAPY OF MEDULLOBLASTOMA OF THE CEREBELLUM. I. LAMPE and R. S. MACINTYRE, Am. J. Roentgenol. **71**:659 (April) 1954.

Lampe and MacIntyre report on 26 patients with proved medulloblastoma of the cerebellum who were treated with x-rays in the period between 1938 and 1946. Of those 26 patients, 7 are still alive. The survival time of these seven living patients varies from 6 to 11 years after the radiation therapy. One patient is a helpless invalid with mental deterioration. Two have convulsive disorders. One patient had an episode of hemiplegia, from which he has now recovered. Three patients are well and show no evidence of disturbance of the brain. All the patients were treated by surgical removal of some of the tumor before x-ray therapy was given. In four of the seven, the surgical removal was known to be incomplete at the time the operation was performed. In three, all of the visible tumor was removed. However, Lampe and MacIntyre point out that there is no substantiated report of a patient living more than three years after surgical removal of a medulloblastoma when no x-ray therapy has been given.

Treatment in most cases consisted of about 1800 r (in air) to each of two posterior skull portals, to each of two lateral skull portals, and to each of two large fields over the upper two-thirds of the spine. A third spinal field was treated with the same dose, and sometimes during the treatment of this third spinal field additional radiation to the posterior skull fields was given. The total dose to each field was given over a period of 7 to 10 days. Generally speaking, this would be considered a rather heavy dose over a short period of time. Lampe and MacIntyre now have changed their treatment method in favor of a protracted course of treatment, in which a larger dose will be given over a considerably longer period of time. They hope that this dosage scheme will prove even more effective than the one that they used to produce seven surviving patients among the 26 patients with medulloblastoma whom they treated. They believe that medulloblastoma is a neoplasm which can be cured by irradiation and that the prognosis need not be as hopeless as it was formerly thought to be.

WEILAND, Grove City, Pa.

NUVARONE (3-METHYL-5-PHENYLHYDATOIN) IN THE TREATMENT OF EPILEPSY. J. H. TATERKA and C. B. THOMPSON, Dis. Nerv. System **14**:108 (April) 1953.

The authors report a clinical trial, in 91 patients, of the antiepileptic substance Nuvarone, which has previously been described as highly effective against induced seizures in experimental animals. Twenty-five patients received the new medication alone; 66 had it combined with another anticonvulsant. Seventy-three had had prior unsuccessful therapy with one or several drugs. The dosage of Nuvarone varied from 1.0 to 3.0 gm. a day, in divided (0.5 gm.) amounts. The response was deemed "fair" (attacks reduced by 35% to 75%) or "good" (attacks reduced by 75% to 100%) in 82 cases (90%). Grand mal and psychomotor illness were benefited in about equal proportions. Petit mal spells were not in any way affected in patients suffering from mixed petit mal and grand mal disease, though the latter component was improved in all. A single case of myoclonus epilepsy was not controlled. Patients with paroxysmal electroencephalograms and diagnoses of migraine and impulsive behavior disorder showed some betterment. No changes in brain wave patterns were noted while patients were taking Nuvarone. Side-effects, mostly mild and transitory, occurred in 19 cases (21%) and included rash, itching, drowsiness, restlessness, headache, abdominal pain, transient loss of taste, mild fever, leucopenia, leucocytosis, and ecchymoses. Though the blood reactions were not severe, they do point up the importance of routine laboratory examinations at regular intervals. Although essentially more toxic than Dilantin, Nuvarone frequently gives better results and has a definite place in the treatment of epilepsy. Unlike the former preparation, it does not appear to cause hypertrichosis, ataxia, or gum hyperplasia.

BEATON, Tucson, Ariz.

Muscular System

STUDIES IN MYASTHENIA GRAVIS. K. E. OSSERMAN, P. TENG, and L. I. KAPLAN, J. A. M. A. **155**:961 (July 10) 1954.

Osserman, Teng, and Kaplan report on their use of a new cholinergic drug, pyridostigmine bromide (Mestinon), which is dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide, an analogue of neostigmine, for the treatment of patients with myasthenia gravis. There have been seven reports in the European literature describing the action of Mestinon on patients with this disease. The consensus of these investigators is that Mestinon is superior to neostigmine.

They note prolonged duration of action and improved general muscle strength, particularly in chewing, swallowing, and eye movements. They also state that there is no abrupt diminution in drug action. One of the most important advantages of Mestinon observed in these studies is the relative absence of undesirable side-effects.

In the present investigation, in a comparative study of neostigmine and Mestinon in equivalent doses (usually 1 Mestinon bromide tablet [60 mg.] for each 15 mg. neostigmine bromide tablet) made on 20 patients with myasthenia gravis, the results obtained with Mestinon were excellent in 9 cases, good in 3 cases, fair in 3 cases, and equivalent to those obtained with neostigmine in 4 cases. The treatment was unsuccessful in one case. The duration of action of Mestinon is only slightly longer than that of neostigmine, approximately one-half hour longer. Mestinon beneficially affects small skeletal muscles innervated by cranial nerves more than the limb muscles of patients with myasthenia gravis. A striking feature of Mestinon therapy is the lack of muscarinic and nicotinic side-reactions.

In general, a 60 mg. Mestinon bromide tablet can be substituted for each 15 mg. neostigmine bromide tablet. In the authors' experience, Mestinon is a superior drug to neostigmine in the treatment of myasthenia gravis and appears to represent an advance in management. However, they point out that neostigmine has withstood the test of time, and further evidence is necessary before Mestinon can be suggested as the drug of choice for the treatment of myasthenia gravis.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

ROENTGENOGRAPHIC EXAMINATION IN MENINGIOMA OF THE TUBERCULUM SELLAE OR OLFACTORY GROOVE. R. D. WEYAND and J. D. CAMP, Am. J. Roentgenol. **71**:947 (June) 1954.

Weyand and Camp summarize the roentgenographic findings which may be present on plain films of the skull to indicate the presence of a meningioma arising from the region of the olfactory groove or the tuberculum sellae. These findings are as follows: (1) formation of an osteoma or hyperostosis in the base of the skull at the point of origin of the tumor; (2) localized erosion of the cribriform plate of the ethmoid bone, the wings of the sphenoid bone, the sulcus chiasmatis, and the tuberculum sellae; (3) erosion of the posterior clinoid processes; (4) enlargement and erosion of the sella turcica; (5) calcification within the tumor itself, and (6) posterior displacement of a calcified pineal gland. Close inspection of good quality roentgenograms is necessary to appreciate these changes.

The roentgenograms of 51 patients having meningiomas arising in the region of the tuberculum sellae were reviewed. Twenty-eight of the patients were found to have hyperostoses in the region of the tuberculum sellae; 8 patients presented roentgenographic evidence of calcification of the tumor; 4 had local erosion which was visible in the lateral and Granger views; sellar erosion was present in 9 cases, and the examinations were normal in 9 patients. Roentgenograms of the skulls of 42 patients having meningiomas arising in the region of the olfactory groove were reveiwed. Sixteen showed hyperostosis, usually in the superior surface of the posterior portion of the ethmoid bone; 6 tumors showed calcification; 3 showed local erosion, and 16 showed erosion of the sella as evidence of extrasellar pressure. Thirteen cases of meningioma of the olfactory groove were suitable for measurement of pineal displacement; 2 of these 13 showed posterior displacement.

WEILAND, Grove City, Pa.

SOME FACTORS WHICH AFFECT THE VALUE OF CAROTID ANGIOGRAPHY IN THE DIAGNOSIS OF BRAIN TUMOR. E. H. WOOD, Am. J. Roentgenol. **71**:952 (June) 1954.

Angiographic localization of a brain tumor depends upon displacement of normal blood vessels or visualization of abnormal blood vessels. The procedure is most frequently successful when the tumor lies near the course of the major branches of the carotid artery. When tumors lie outside the distribution of the larger carotid arterial branches, the method usually fails to diagnose them. The highest effectiveness of the method is obtained when it is applied to those patients in whom there is reason to believe there is a tumor located near the major carotid branches and when it is not applied to patients whose tumors are thought to be located rather far away from the major carotid branches. Wood reviewed the case histories of 100 consecutive patients for whom a diagnosis of brain tumor was made and later verified. All these patients had cerebral angiograms. In 81 of them the angiogram, interpreted strictly objectively, diagnosed the loca-

tion of the tumor. In 19 patients the angiogram failed to reveal evidence of an abnormality. All frontal and suprasellar tumors were correctly diagnosed by this method. Only 2 out of 25 temporal tumors were missed. However, 8 of 10 parietal tumors were not diagnosed; 4 of 4 occipital tumors were missed; 4 of 4 thalamic tumors were missed, and 1 posterior fossa tumor was missed. One tumor of the corpus callosum was corectly diagnosed.

The most important guide in selection of patients for cerebral angiography is thorough clinical neurologic examination. When this examination leads one to suspect a mass lesion in the frontal, suprasellar, or temporal region of the brain, a cerebral angiogram is indicated. If a visual field examination suggests a lesion in the vicinity of the optic chiasm, cerebral angiography will probably be helpful. Patients whose plain skull films show enlargement of the sella turcica or show hyperostosis of the skull, bone erosion, or abnormal intracranial calcification near the normal course of the branches of the internal carotid artery are suitable candidates for carotid angiography. Patients whose plain films of the skull show backward, downward, or lateral displacement of the pineal gland are usually suitable for cerebral angiography. Upward or forward displacement of the pineal gland usually indicates the presence of a mass in a location which will not be diagnosed by cerebral angiography.

WEILAND, Grove City, Pa.

RUPTURE OF AN ANEURYSM OF THE INTERNAL CAROTID ARTERY DURING CEREBRAL ANGIOGRAPHY. E. L. JENKINSON, O. SUGAR, and H. LOVE, Am. J. Roentgenol. **71**:958 (June) 1954.

Jenkinson and his associates report the case of a 49-year-old woman who died about 30 hours after cerebral angiography had been performed, apparently because of rupture of an aneurysm of the internal carotid artery into the subarachnoid space. The patient had a history of periodic headaches for many years, the last of which was severe and was associated with a stiff neck. She developed another headache, collapsed, and became cyanotic and comatose. A lumbar puncture showed blood in the spinal fluid. Three days later she was more alert and was transferred to another hospital for a cerebral angiogram. This study was performed satisfactorily in the left common carotid artery and then was attempted in the right. Four different attempts to place the needle correctly in the right common carotid artery were unsuccessful. On the fifth attempt the right internal carotid artery was filled to the region of the siphon, but none of its intracranial branches were demonstrated in the single film which was made. The artery seemed narrow in the neck, thought to be the result of arteriosclerosis. The artery could be seen up to the region of the anterior clinoid process in the skull, at which point its continuity was lost. The contrast medium was seen outside the normal cerebral vascular tree. The pattern of the extravasated contrast material suggested that it was located in the basal cisterns of the subarachnoid space.

Immediately after the "successful" injection of the right internal carotid artery the patient stopped breathing. An irregular type of respiration was started after a period of artificial respiration, but the patient never recovered consciousness. She had fever, irregular blood pressure, and an irregular pulse, and died about 30 hours after the cerebral angiography had been performed. No autopsy was obtained.

WEILAND, Grove City, Pa.

ROENTGEN MANIFESTATIONS OF EPIDURAL GRANULOMAS OF THE SPINE. J. H. CAMPBELL and R. A. SILVER, Am. J. Roentgenol. **72**:229 (Aug.) 1954.

Campbell and Silver report the clinical and roentgenologic aspects of 10 cases of epidural granuloma of the spine. This lesion produces boring and often severe back pain. There is usually clinical evidence of infection, radiculitis, and spinal cord damage. Early diagnosis is important so that the disease can be treated before extensive and permanent damage to the cord occurs.

Epidural granulomas occur as a complication of vertebral osteomyelitis or by direct extension from an infection adjacent to the vertebral column. They arise more commonly when the osteomyelitis involves the neural arch, since there is a larger subdural space posteriorly. Plain films of the spine will often demonstrate the osteomyelitic process. The presence of a paraspinal soft tissue mass in patients presenting clinical evidence of an epidural lesion usually denotes an underlying osteomyelitis of the vertebrae despite the fact that roentgen changes in the bone cannot be demonstrated. Laminograms of the spine are valuable to demonstrate small destructive changes in the spine that the plain films do not demonstrate. Myelograms are very important in the diagnosis of epidural granuloma. Campbell and Silver believe all these patients will present some abnormality in the myelogram. Positive myelographic findings frequently are present in acute cases before bone or soft tissue changes become demonstrable in the plain roentgenograms.

WEILAND, Grove City, Pa.

Books

Psychosurgery and the Self. By Mary Frances Robinson and Walter Freeman. Price, $3.00. Pp. 118. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

This is a psychologist's study of 76 patients undergoing lobotomy and of 17 control subjects. Both groups were stabilized and functioning effectively in the community from four months to ten years or more after release from the hospital. What is it that distinguishes lobotomized people from others who have not had an operation? It is not the I. Q. or ability to run the Porteus maze. Deliberation tests are not truly significant. Rather, it is the relationship of the patient to himself. This feature has been tested in a number of ways. The Self-Regarding-Span is the number of seconds that a patient can be brought to examine and scrutinize himself for the benefit of the examiner. In addition to the simple matter of time, there is also the quality of the responses, with the amount of concern or detachment expressed. Finally, a sensibility questionnaire attempts to elicit the reaction of the patient to situations, real and imagined, in the past, present, and future. In all these fields the lobotomized patient shows up as definitely altered in the direction of brief response, detachment, and insensitivity. *P* values are calculated at less than 0.001. There is, in addition, a quantitative relationship between the lowered scores and the extent of the surgical operation, again with a *P* factor of 0.001. For instance, on the sensibility questionnaire, control patients score +7; transorbital lobotomy patients score —5; minimal lobotomy, —7; standard lobotomy, —9, and radical lobotomy, —13. That the findings are not accounted for by the original disorder is revealed in two patients operated upon for pain, whose performance on the usual psychologic tests was excellent, but whose self-functions were extraordinarily impaired after operation. "The recent remarkable success of transorbital lobotomy in restoring many patients to health without distressing personality changes may well render the more drastic operations obsolete. Yet these drastic operations with unfortunate sequelae, however discouraging to the physicians in charge, are extremely valuable from the point of view of psychological research. Psychosurgery has performed a sort of beneficient vivisection, revealing the relations between amount of intact frontal lobe and levels of integration and development. . . . Standard prefrontal lobotomy produces a good deal of early confusion, but after a few months or years, many patients make good adjustments to the present on a somewhat less complex scale than before, since they are free of complicating worries. As Case 187 said, 'I never think about the past; it's too long ago."

"A few extremely favorable cases . . . indicate that it is possible for surgery to reduce some of the complex hierarchies underlying self-continuity just enough to interrupt and destroy the vicious circle of disease; for these people have become effective personalities again, with lessened need for introspection and increased cheerfulness of outlook."

Studies in Schizophrenia: A Multidisciplinary Approach to Mind-Brain Relationships. By Robert G. Heath, Editor. Price, $8.50. Pp. 619, with illustrations, charts, and tables. Harvard University Press, Cambridge 38, Mass., 1954.

Heath has focused attention of psychosurgery on the septal area, that part of the brain lying close to the midline in the neighborhood of the anterior commissure. It has been known for some time that lesions in this area produced considerable apathy and inertia, along with visceral phenomena. The first step was to verify these findings in animals, and then to apply various methods of intervention in schizophrenics with the idea of rousing them from their preoccupations. This is a major study, and the findings bring some support to the idea that in this region is the cephalic representation of the reticular formation, with its alerting response upon stimulation. Many difficulties were encountered in the stereotaxic placement of the electrodes used for stimulation, but the placement was more satisfactory by this means than by direct implantation. Recordings taken from the areas at the base of the brain and from neighboring spots showed how different are the electrical manifestations than are those as customarily taken from electrodes placed upon the scalp. The highlights of this research were the demonstration that spike foci appeared in deep electrodes in certain schizophrenic patients that were not present in patients suffering from painful and other conditions. Furthermore, there was definite arousal on stimulation of certain points, an arousal that was sometimes maintained to the point of effective restoration to life outside a hospital.

This volume is particularly interesting because it presents, in addition to the detailed description of the project, the critical comments of a number of topflight investigators who were invited

to a three-day conference on the subject. Among these investigators there is little unanimity, since the viewpoints range all the way from electronics to psychoanalysis, but the criticisms are constructive, even though they require strict attention on the part of the reader. Allowing for the discrepancies, the varied clinical material, the complications, and the limited follow-up, this work represents an earnest attempt to apply the techniques of neurophysiology to the mental and emotional problems found very frequently in the forefront of psychiatric investigations.

O sistema hipocampo-talamo-cingular. By J. M. Vianna. Price, not given. Pp. 68, with 9 figures and 1 table. Tipogr. Benedetina, Bahia, Argentina, 1954.

There are just enough interesting results in patients with epilepsy and conduct disorders to make this monograph worth while. However, the author concludes: "The observed facts are not sufficient to confirm the theoretical conceptions and hypotheses that were the point of departure of the investigations undertaken." There is a long chapter on the anatomy of the rhinencephalon and its connections, which, however difficult to present to the reader in a three-dimensional pattern, arrives at the conclusion that the hippocampal formation is in no way concerned with the olfactive process. Stimulation of the anterior part of this structure produced uncontrollable movements with partly formed speech, which was of compulsive character and not intentional on the part of the patient. Stimulation of the posterior part produced some changes in vital signs, quite transient. Extirpation of the hippocampus produced no significant alterations in the neurologic picture, and nothing of note psychiatrically in the majority of the 37 patients reported upon. In a few young patients with epilepsy and difficult conduct disorders there was remarkable change for the better, although others remained unaffected. Cingulectomy in six patients resulted in three improvements. Bilateral operations seemed more favorable than unilateral, and extirpations, more effective than simple undercutting, whether in the cingulum or in the hippocampus. The removal of the hippocampus by aspiration throws some doubt upon the specificity of the operation, since some of the medial temporal cortex may easily have been included. Furthermore, a 3 cm. incision through the second temporal convolution may also have had an additive effect.

Some Problems in Neurophysiology. By Frédéric Bremer. Price, 21s. Pp. 73, with 32 illustrations. The Athlone Press, University of London, Senate House, London, W.C. 1: John de Graff, Inc., 64 W. 23d St., New York 10, 1953.

In May, 1950, Prof. Frédéric Bremer gave three lectures at the University of London, which are now published. In the first, "Synaptic Transmission, Inhibition, and Auto-Rhythmicity in the Spinal Cord," reference is made to the concept that incoming impulses set up depolarization of the nerve cell, spreading electronically along the axon. Excitation and inhibition are discussed in terms of polarization changes and the role of chemical mediators. Autorhythmicity in the spinal cord is believed to find support in properties of reflex after-discharge, postural contraction, and oscillography.

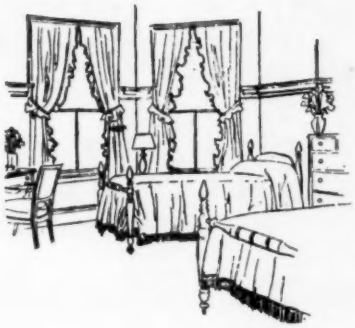
The lecture on "Physiological Basis of Electroencephalography" deals with isolated whole brain and cerebrum preparations. Concepts of reverberating circuits and electrotonic changes are explored in explaining arousal effects, inherent rhythmicity, and the nature of the functional sign of spontaneous electrical activity.

In "The Auditory Area of the Brain: An Oscillographic Study of Its Activity," Bremer summarizes the evidence for localization of the primary and secondary auditory areas and interprets the responses to clicks and pure tones in terms of intracortical phenomena. Responses in distant areas may indicate a basis for perceptual integration.

Brief mention of advances in these fields up to and including 1952 is made in a supplementary note. The usual lucid expositions of Professor Bremer are again found here, so that even those whose chief fields of interest are not in neurophysiology can read these lectures with profit.

CORRECTION

In the article "Intravenous Hydrocortisone, Corticotropin and the Electroencephalogram," published in the March issue, page 338, a subtitle "Effects in Epileptics and Nonepileptics" was inadvertently omitted. Further, the sentence beginning on line 11 of the second column on page 342 should read as follows: "It is also conceivable that the electroencephalographic abnormalities present in patients with Addison's disease may be a function of high serum adrenocorticotropic hormone[18] rather than low steroid levels."



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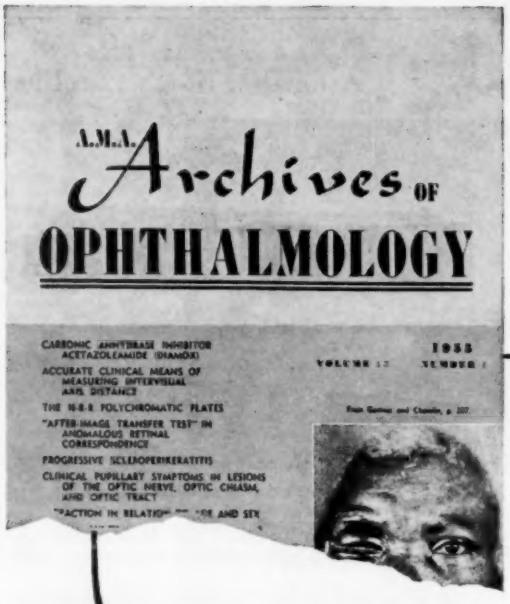
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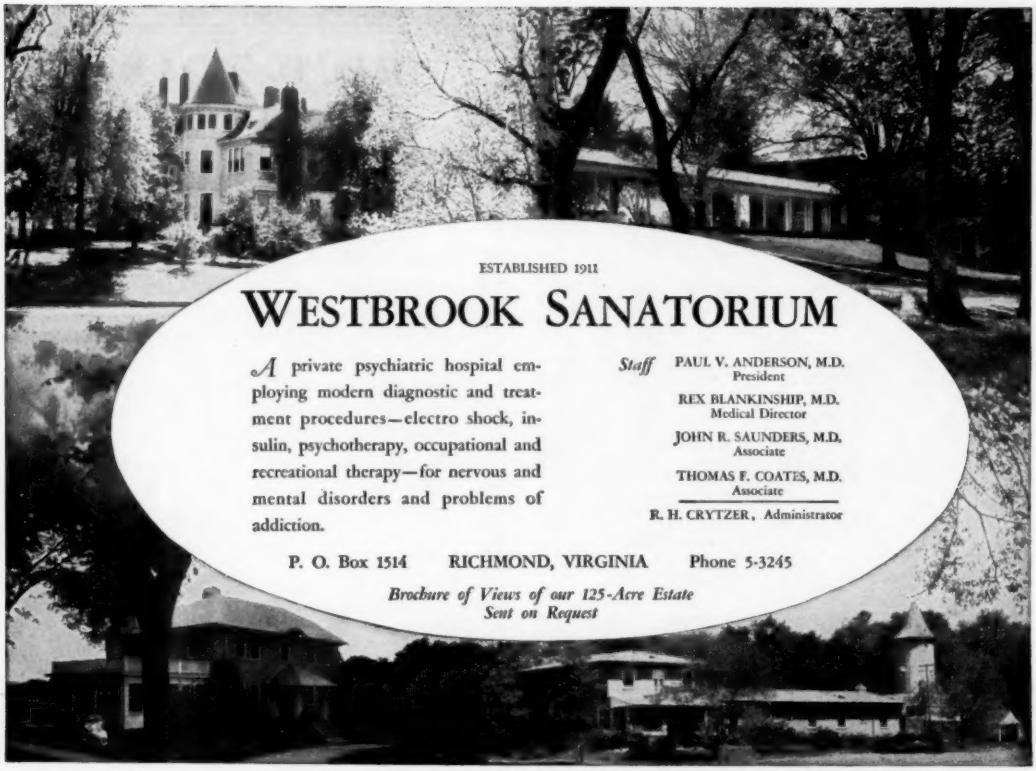
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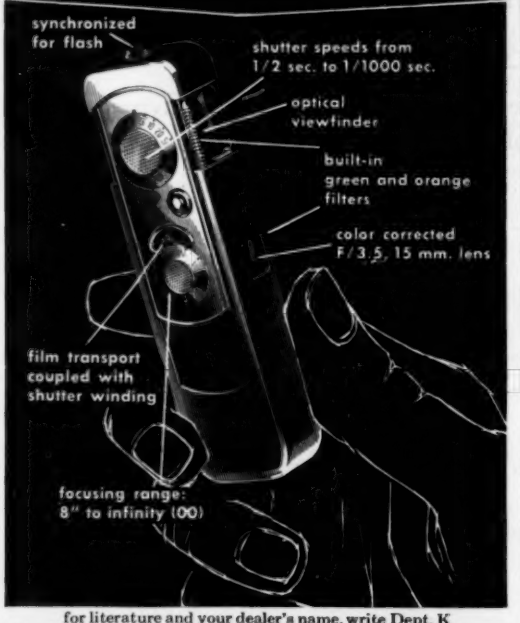
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